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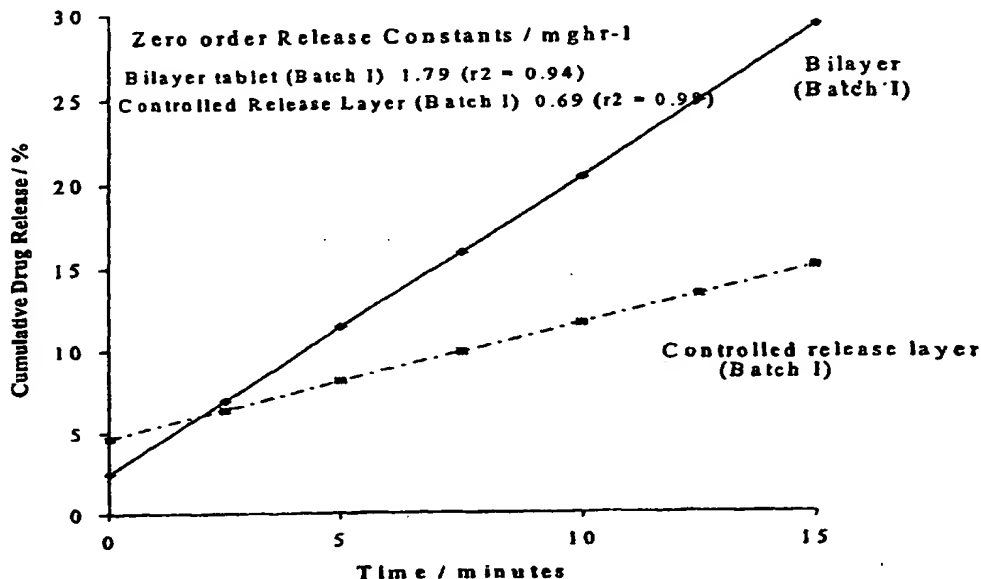
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(54) Title: **BILAYERED BUCCAL TABLETS COMPRISING NICOTINE**



(57) Abstract: A method of delivering substance, e.g. a drug, to a subject comprises attaching a tablet or other dosage form to a buccal mucosa, where the dosage form is adapted to release the substance in a multiphasic manner, typically with an initial burst release of substance followed by controlled release over a longer period. The substance is typically nicotine.

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BILAYERED BUCCAL TABLETS COMPRISING NICOTINE

1

2

3 This invention relates to the delivery of substances
4 such as bio-active agents and pharmaceuticals to the
5 body. In a preferred embodiment the invention
6 concerns the delivery of nicotine to the buccal area.

7

8 Nicotine replacement therapy (NRT) is a frequent
9 component of strategies to help smokers stop smoking.
10 Present NRT delivery systems include chewing gum and
11 transdermal patches which release the drug over a
12 period of time but do not provide an initial surge of
13 rapidly released drug that mimics the effect of
14 cigarette inhalation; nasal sprays and inhalers are
15 also available which deal with this problem, but
16 these methods do not permit long term release.

17

18 According to the present invention there is provided
19 a method of delivering a substance to the buccal
20 mucosa of a subject, the method comprising providing
21 a tablet comprising a quantity of the substance to be
22 delivered, the tablet having multi-phasic release

1 properties to release controlled amounts of the
2 substance to the subject over time, and releasing the
3 substance from the tablet in the subject's mouth.
4 The invention also provides a tablet for delivery of
5 a substance to the buccal mucosa of a subject, the
6 tablet comprising a quantity of substance to be
7 delivered to the subject, the tablet having multi-
8 phasic release properties adapted to release
9 controlled amounts of the substance to the subject
10 over time.

11

12 The tablet can be of conventional physical design but
13 any vehicle capable of bearing the substance and
14 dissolving in the mouth can be used.

15

16 The tablet may have a multi-layer structure with
17 different amounts of substance associated with each
18 layer. This can be by making different homogeneous
19 layers with different release characteristics or by
20 enclosing different quantities of substance within
21 layers of e.g. coating that can dissolve at different
22 rates, thereby deferring the time until the fluids in
23 the mouth dissolve the substance and/or the tablet
24 matrix.

25

26 The tablet may comprise a bioadhesive such as
27 Carbopol(TM) or chitosan, or a similar bioadhesive
28 polymer, and this can optionally be in a separate
29 adhesive layer, or can be incorporated into another
30 part of the tablet, such as the slow (or controlled)
31 release layer. The inventors have found that these

1 compounds also assist in controlling the release of
2 the substance. The tablet may also contain other
3 agents to control the release of the substance such
4 as hydroxypropylmethyl cellulose, hydroxypropyl
5 cellulose, poly D L lactide- and/or glycolide-
6 related polymers. Such polymers are very useful in
7 the present invention as they swell when hydrating
8 and this can be used to control the release
9 characteristics of the substance which is retarded in
10 the swollen polymer until the polymer starts to
11 dissociate from the tablet. This can be used to
12 change the release characteristics of the tablet
13 without necessarily changing the amount of substance
14 in the tablet, and without layering the tablet. Thus
15 multi-phasic release properties can be achieved with
16 a homogeneous tablet.

17
18 The outer layer of the tablet may be adapted to
19 release a quantity of the substance very quickly to
20 satisfy a craving in the subject for addictive
21 substances.

22
23 Typically the substance is nicotine. Other
24 substances are also suitable such as cannabinoids,
25 antibiotics, analgesics or anaesthetics such as
26 lidocaine for direct application to mouth ulcers etc
27 or for use prior to or following dental treatment,
28 and drugs for other buccal infections. In principle,
29 any drug that is suitable for oral administration can
30 be used in the present invention.

31

1 Excipients that assist in the penetration of the
2 substance through the buccal membrane can be
3 included, such as bile salts.

4
5 The inner layer or layers may be associated with
6 slower release of substance. The layers may contain
7 the substance as an integral component of the layers
8 or the substance may be provided in a separate layer
9 beneath coatings that exhibit the desired release
10 characteristics. For example, the layers may be made
11 up of a material that is adapted to dissolve at a
12 known rate so as to release the substance underneath
13 the layer or trapped within it at a set time after
14 the tablet is placed in the mouth.

15
16 Preferably different layers have different release
17 characteristics. For example the outer layers are
18 preferably capable of releasing substance at a
19 different (preferably faster) rate than the inner
20 layers.

21
22 In a preferred embodiment the tablet formulation
23 consists of two distinct layers, each of which has a
24 specific function. A controlled release layer
25 containing a bioadhesive is attached to the mucosal
26 tissue lining the cheek adjacent to the gum (gingiva)
27 in the buccal area of the patient's mouth. Upon
28 contact with saliva the rapid release layer
29 disintegrates and releases nicotine, which is
30 subsequently absorbed through the oral mucosa into
31 the systemic circulation. This immediate release and

1 absorption of nicotine is designed to reduce or
2 eliminate the cravings for nicotine of the smoker,
3 particularly those following a meal (post-prandial
4 cravings). The time period over which the tablet
5 remains attached to the buccal mucosa typically
6 determines the time period over which nicotine is
7 released. This is potentially up to three or four
8 hours. During this period nicotine is being absorbed
9 into the systemic circulation at a constant rate
10 (referred to as zero order release), independent of
11 the amount of nicotine remaining in the formulation,
12 thus eliminating further cravings for nicotine. The
13 user may, at any time, detach and remove the tablet
14 if they think this appropriate. One possible scenario
15 of usage is removal of the tablet prior to eating a
16 meal followed by attachment of a new tablet following
17 completion of the meal.

18
19 Various doses of nicotine or other substance can be
20 incorporated into the tablet, in both the rapid and
21 controlled release layers, thus allowing flexibility
22 in reducing regimes for patients and tailoring the
23 formulation to individual patterns of craving for
24 nicotine. The incorporation of different doses of
25 drug does not alter the release mechanism; i.e. it
26 remains rapid from the first layer and zero order
27 from the controlled release layer.

28
29 Typical dimensions of the tablet are 6mm diameter and
30 3mm thickness. These dimensions are usefully
31 independent of nicotine or other substance content as

1 any reductions in the same are compensated for by
2 increased amounts of diluent to maintain tablet
3 weight and dimension.

4
5 For mucoadhesion, Carbopol C934 has been extensively
6 studied and been shown to produce excellent adhesion
7 to mucosal membranes. The bioadhesive strength of
8 this poly (acrylic) acid polymer increases with
9 polymer concentration up to 25% w / w and thereafter
10 remains relatively constant and a tablet containing
11 5-50 % C934 can adhere to the gingiva for 550-600
12 minutes. C934 was therefore favoured as the
13 mucoadhesive polymer in the formulation at a
14 preferred concentration of around 20 % w / w where
15 mucoadhesive strength is near maximum and below the
16 50 % concentration, which has the potential to cause
17 some mucosal irritation.

18
19 For controlled drug release from buccal adhesive
20 tablets, HPC is effective in producing controlled
21 drug release.

22
23 The layers of the tablet need not be concentric
24 although in certain embodiments this is preferred.
25 In certain embodiments shown in the examples
26 following the tablet has two (or more) flat layers in
27 a "sandwich" structure.

28
29 Examples of the invention will now be described by
30 way of illustration, and without limiting the scope

1 of the invention, with reference to the accompanying
2 drawings, in which:

3 Fig. 1 is a schematic view of a tablet;
4 Fig. 2 is a graph of representative nicotine
5 release profiles from dosage forms;
6 Fig. 3 is a diagrammatic representation of drug
7 release from a polymer matrix;
8 Fig. 4 is a graph of release of nicotine from a
9 bi-layer tablet;
10 Fig. 5 is a schematic diagram of diffusion
11 apparatus used in the methods described;
12 Fig. 6 is a graph of water uptake profiles for
13 buccal adhesive tablets;
14 Fig. 7 is a graph of NHT dissolution profiles
15 for buccal adhesive formulations;
16 Fig. 8 is a graph of diffusional exponent values
17 for nicotine buccal adhesive tablets;
18 Fig. 9 is a graph of NHT kinetic rate constant
19 values for nicotine buccal adhesive tablets;
20 Fig. 10 is a graph demonstrating the linear
21 relationship between NHT release rates and HPC
22 content of nicotine buccal adhesive tablets
23 using diffusion dissolution apparatus;
24 Figs. 11 and 12 are graphs showing dissolution
25 profiles for bilayer tablets; and
26 Fig. 13 shows drug release profiles of NHT
27 bilayer tablets over the first hour of a 4 hour
28 flow through dissolution test.

29

30 Example 1.

31

1 Controlled release formulations A - F were produced
2 as shown in Table 1.1, containing nicotine in the
3 form of NHT, PVP to act as a binding agent, lactose
4 as a diluent and magnesium stearate as a lubricant.
5 C934 was included to impart adhesive properties and
6 HPC was included in a range of concentrations to
7 investigate its effect on NHT release. PVP (molecular
8 weight 44000) is included as a binding agent, but
9 also has release-controlling properties.
10 Carbopol(TM) 934P is a synthetic high molecular
11 weight cross-linked polymer, which imparts
12 bioadhesive properties on the formulation. In
13 addition this polymer also has release-controlling
14 and binding properties.
15
16 Spray-dried lactose is included as an inert diluent.
17 The physical and chemical properties of this material
18 are ideal for use as such an agent.
19
20 HPC is a semi-synthetic polymeric cellulose
21 derivative which has matrix-forming properties. Once
22 hydrated the drug can diffuse out of the matrix.
23 This material thus has drug release controlling
24 properties.
25
26 Magnesium stearate was optionally added as a glidant
27 and anti-adherent agent which facilitates powder flow
28 (essential for successful tablet production) and
29 prevents adherence of the powder materials to the
30 tooling of the tablet manufacturing apparatus.
31

1 **Table 1.1.** Excipient concentrations used in the
2 preparation of formulations A - F.

<i>Excipient composition of tablet mg / tab</i>						
	A	B	C	D	E	F
NHT	10	10	10	10	10	10
PVP (44,000)	6	6	6	6	6	6
C934	20	20	20	20	20	20
HPC	-	10	20	30	40	50
SDL	63	53	43	33	23	13
MGS	1	1	1	1	1	1

3 NHT = nicotine hydrogen tartrate, PVP = polyvinylpyrrolidone, C934 =
4 carbopol, HPC = hydroxypropylcellulose, SDL = spray dried lactose
5

6 The excipients were weighed accurately and physically
7 mixed by shaking in a bag for 10 minutes. Powder
8 mixes were used to produce 100 mg tablets by direct
9 compression using an eccentric tablet press (model
10 F3, Manesty machines Ltd, Liverpool, UK) using 6 mm
11 punches.

12
13 The dose of nicotine may be varied depending on
14 requirements and a corresponding reduction in
15 mannitol amount maintains tablet dimensions constant.
16 The RRL is optionally formed by mixing the above
17 ingredients and compressing them in a mould of
18 desired shape to form the layer.

19
20 Bilayer nicotine buccal tablets were formulated.
21 Burst release of NHT from a rapid release layer to
22 satisfy a craving for nicotine, followed by prolonged
23 release of nicotine from a controlled release layer
24 to prevent reoccurrence of the nicotine cravings.

1 Rapid release layers (RRL) were formulated using the
2 excipients listed in table 1.2

3

4 **Table 1.2.** Excipient concentrations used in the
5 preparation of RRL layers for bilayer tablet
6 manufacture.

<i>Excipient composition of rapid release layer mg / layer</i>		
	<i>2 mg RRL</i>	<i>5 mg RRL</i>
NHT	2	5
PVP 10,000	4	4
Mannitol	44	41

7

8 The excipients were again physically mixed in a bag
9 for 10 minutes. Bilayer tablets were produced using
10 a 2-stage compression cycle. The controlled release
11 layer (CRL) was first formed by direct compression of
12 powder mixes A - F in table 1.1. The CRL was left in
13 the tablet die and the bottom punch lowered. 50 mg of
14 the RRL was added to the die and the second
15 compression carried out. The bilayer tablets were 6
16 mm x 4.5 mm in dimension and are depicted in figure
17 1. Bilayer tablets containing both 2 mg and 5 mg RRL
18 were prepared with each CRL (A - F).

19

20 The RRL could be distinguished from the CRL layer by
21 the pure white colour of the RRL through the use of
22 mannitol. In a marketed product, the addition of a
23 pharmaceutical pigment would allow the user to
24 distinguish the layers and identify which layer
25 should be attached to the gingiva (gum).

26

27 Example 2.

1 In this example the RRL was as described in example 1
2 above, and the CRL was as follows:

3

4 Table 2

5

Amount per tablet / mg (percentage composition)		
Ingredient	CRL 2	
Nicotine	10	(10%)
Magnesium stearate	1	(1%)
PVP*	10	(10%)
Carbopol (TM) 934P	20	(20%)
Spray-dried lactose	19	(19%)
HPC**	40	(40%)

PVP = polyvinyl pyrrolidone, molecular weight 44000.

6 ** HPC = hydroxypropyl cellulose. In each example, the two
7 layers of the overall tablet were separately
8 fabricated; although combined fabrication of whole
9 tablets is generally within the scope of a skilled
10 man. In the present examples the RRL ingredients
11 were mixed and granulated using ethanol as the
12 granulating fluid, followed by compression into
13 tablets; for the CRL the ingredients were dry mixed
14 and tablets formed by direct compression. The two
15 individual tablet layers were then replaced in the
16 die of a tablet press and compressed for a second
17 time, resulting in the formation of one coherent
18 bilayer tablet.

19

20 The tablet manufacturing apparatus employed for the
21 fabrication was a standard single punch eccentric
22 press with no modifications. For the rapid production

1 of larger batches of product a specialised double
2 compression tablet press can be used.

3
4 Results for examples 1 and 2.

5
6 Using standard BP disintegration apparatus it was
7 found that the rapid release layer completely
8 disintegrated within four minutes. This time is
9 considered acceptable to facilitate rapid absorption
10 of nicotine from the oral mucosa thus eliminating the
11 initial craving of the smoker for nicotine.

12
13 The nicotine release from the formulations produced
14 was studied over a four-hour period using standard
15 USP paddle dissolution apparatus and a typical
16 release profile of the results obtained is depicted
17 in Figure 2.

18
19 The drug release profiles demonstrate the biphasic
20 nature of the release from the bilayer formulations:
21 an initial burst release of nicotine followed by
22 retarded zero order drug release. This characteristic
23 is absent from the single layer controlled release
24 tablets, which release drug in a monophasic zero
25 order kinetic manner. The initial burst nicotine
26 release is essentially complete within 30 minutes.
27 This result contradicts the disintegration time of
28 the RRL of 4 minutes. However, differences in the
29 hydrodynamic properties of the two test methodologies
30 account for such contradictory results; nonetheless,
31 it is believed that the faster release initially

1 would sufficiently satisfy initial craving rapidly,
2 and encourage buccal absorption, rather than the
3 swallowing of saliva and consequent unpleasant
4 gastro-intestinal effects.

5
6 The mechanism by which drug release is retarded in
7 the controlled release formulations is thought to be
8 due to the formation of a matrix of drug and
9 polymer(s) during fabrication and subsequent contact
10 with the dissolution medium. The drug is evenly
11 dispersed within this matrix, as shown in Fig 3. The
12 dissolution medium can enter through pores in the
13 matrix, dissolve the drug and the resulting drug
14 solution diffuses out of the matrix.

15
16 This type of mechanism normally results in first
17 order drug release, as diffusion is a first order
18 process, i.e. the rate of diffusion is dependent on
19 the amount of drug remaining in the formulation. The
20 observation of zero order drug release from the
21 formulations produced is thought to be due to a
22 complex combination of drug diffusion, matrix erosion
23 and interaction of oppositely charged nicotine
24 (cationic) with anionic substituent groups on the
25 Carbopol(TM) molecule, i.e. the -COOH groups.

26
27 Example 3

28
29 Table 3.1 below shows the formulation ingredient
30 quantities of the controlled release layer of further
31 embodiments A-I. The rapid release layer contained 2

1 mg NIC, 4 mg PVP 10000 and 44 mg mannitol. The two
2 layers were produced individually by direct
3 compression (8mm punch). Bilayer tablets were
4 produced by manually compressing the two layers
5 together (Manesty F3, Liverpool, UK).

6
7 **Table 3.1**

<i>Sustained release layers produced.</i>									
<i>Mass of ingredient per tablet / mg</i>									
<i>Tablet Formulation Number</i>									
	A	B	C	D	D	F	G	H	I
Ingredient									
NIC	10	10	10	10	10	10	10	10	10
Carbopol	20	20	20	20	20	20	-	-	-
934 (r)	2	4	6	2	4	6	2	4	6
PVP 44000									
HPC	-	-	-	40	40	40	40	40	40
MgS	1	1	1	1	1	1	1	1	1
LactoseTO	100	100	100	100	100	100	100	100	100

PVP = polyvinylpyrrolidone, HPC = hydroxypropylcellulose*

MgS = magnesium stearate

* HPMC can also be used

9
10 In vitro drug release was assessed using a
11 dissolution cell method in which the tablet was
12 attached to an artificial dialysis membrane, used to
13 simulate the buccal mucosa, and the drug was released
14 through this into a reservoir of distilled water, and
15 determined by UV spectrophotometry. Other methods
16 used included USP paddle dissolution methods. Zero
17 order release profiles were achieved for batches A-I

1 over 4 hours. The following table 3.2 demonstrates
2 batches G-I had the highest release rates due to the
3 absence of Carbopol 934P(r). Release rates were
4 decreased in all batches by increasing concentrations
5 of PVP which resulted in decreased layer swelling.

6 **Table 3.2**

7

<i>Zero order release rates of nicotine (diffusion cell)</i>					
Formulation	A	B	C	D	E
Dissolution	0.26	0.17	0.15	0.25	0.15
Rate / % min-1					
Formulation	F	G	H	I	
Dissolution	0.12	0.37	0.35	0.37	
Rate / % min-1					

8 Equation 1, an exponential expression used to analyse
9 controlled release behaviour of pharmaceutical
10 systems, was employed to investigate the dissolution
11 data (Peppas and Sahlin, 1989 Int. J. Pharmaceutics
12 57:169-172).

13

14 $M_t / M_\infty = kt^n$ - Equation 1

15

16 In this equation, M_t / M_∞ is the fraction of drug
17 released, k is the kinetic constant and n is the
18 diffusion exponent for drug release. This equation
19 can be applied to the first 60 % of drug release to
20 identify the type of drug release from the system. A
21 plot of $\log (M_t / M_\infty)$ versus $\log t$ gives a straight
22 line of gradient n and intercept $\log k$.

23

1 Diffusion cell results ($n = 0.69-0.93$) indicated the
2 overall drug release mechanism was non-Fickian
3 controlled by a combination of NIC diffusion and
4 polymer chain relaxation ($r^2 = 0.88-0.97$).

5
6 Fig. 4 shows release profiles from tablets (US
7 paddle) and demonstrates the efficient release from
8 the rapid release layer of sample I (98% of the
9 nicotine was released after 10 minutes).

10 Example 4

11 Dosage forms formulated as above were tested to
12 ensure that the patient receives a product containing
13 the required amount of drug substance in a form that
14 enables the drug substance to exert its full
15 pharmacological action. The standard tests included
16 uniformity of weight, uniformity of content,
17 disintegration (where appropriate) and dissolution,
18 and the non-standard crushing strength and resistance
19 to abrasion tests.

20
21 Ten tablets from each tablet batch were selected and
22 weighed accurately to 4 decimal places using an
23 analytical balance (model AE 50, Mettler instruments
24 LTD, High Wycombe, U.K.). The tablet weights were
25 averaged and a relative standard deviation value
26 calculated.

27
28 Three tablets from each batch were weighed and the
29 theoretical NHT content was calculated. Each tablet

1 was then powdered and placed in a standard flask and
2 allowed to dissolve in 50 mL of HPLC mobile phase.
3 To facilitate the solution of the water swellable
4 polymers within the tablet matrix, and ensure
5 complete NHT release from the polymers, the flasks
6 were placed in an ultrasonic bath for 60 minutes,
7 left overnight and then placed in the sonic bath for
8 a further 60 minutes. The solutions were filtered
9 under gravity using filter paper, diluted
10 appropriately and the NHT content assayed using an
11 analytical HPLC method.

12

13 The crushing strength test involves application of a
14 compressive load to the tablet to induce breaking.
15 Sophisticated testers apply the force at a constant
16 rate to improve reproducibility over simple hand
17 operated devices. However, even when the load is
18 applied at a constant rate, the variation in strength
19 within a batch may be considerable.

20

21 Five tablets from each batch were placed in a tablet
22 hardness tester (model TBH 28, Erweka, Heusenstamm,
23 Germany). The values were averaged and a relative
24 standard deviation value was calculated.

25

26 It is likely that a tablet, during a normal life,
27 will be exposed to forces in production, packaging or
28 transportation procedures. These forces whilst not
29 severe enough to break the tablet, may abrade small
30 particles from its surface. To assess the resistance
31 to abrasion, a friability tester is used, which

1 subjects tablets to a uniform tumbling action, for a
2 specified time, and the weight loss from the tablets
3 is measured.

4
5 Five tablets from each batch were weighed
6 collectively and the weight noted. The tablets were
7 then placed in a friability tester (model TA, Erweka,
8 Heusenstamm, Germany). After 5 minutes, the five
9 tablets were re-weighed and the percentage weight
10 loss was calculated.

11
12 A swellable matrix is used to control the release of
13 drug, and polymer swelling is an important stage in
14 the formation of a mucoadhesive bond between such
15 formulations and the mucosa. *In vitro* swelling
16 studies were therefore carried out.

17
18 Three tablets from each batch were placed on a
19 plastic mesh (1 cm²) to allow handling of the tablet
20 without direct touching. The tablet / mesh assembly
21 was weighed accurately to 4 decimal places and the
22 weight noted. The axial and radial dimensions of the
23 tablets were measured using sliding scale callipers.
24 Each tablet assembly was placed in separate glass
25 vials containing 4 ml of deionised water. At
26 specific time intervals over 24 hours, the tablet
27 assembly was removed from the vials and any surface
28 moisture was carefully removed using filter paper.
29 The assembly was re-weighed and the axial and radial
30 dimensions were again noted. The percentage increase

1 in weight, axial and radial dimensions was
2 calculated.

3
4 *In Vitro* NHT dissolution was analysed using two
5 different methods. The first involved flow through
6 dissolution apparatus, where the buccal adhesive
7 tablets were exposed to 20 mL dissolution medium.
8 The second method is a novel method, devised to more
9 accurately represent the *in vivo* conditions to which
10 a buccal adhesive tablet might be exposed. The
11 method used a transdermal tester and following NHT
12 dissolution from the tablet in a small volume (< 0.5
13 mL) the detected NHT diffuses across a membrane in to
14 a 5 mL cell.

15
16 Three tablets from each batch were weighed and the
17 theoretical nicotine contents were calculated and
18 noted. The tablets were placed separately in a 20 mL
19 cell in the flow through dissolution tester. The
20 dissolution medium was distilled water supplied at a
21 flow rate of 100 mLhr⁻¹ by a pump (model 202u, Watson
22 - Marlow, Falmouth, U.K.) and at 37°C from an
23 electric water heater (model W14, Grant Instruments,
24 Cambridge, U.K.). The effluent from the cells was
25 collected over a 4 hour period and assayed at certain
26 time intervals using U.V. detection at 259 nm (model
27 UV 300, Unicam LTD, Cambridge, U.K.).

28
29 A transdermal tester as shown in Fig. 5 (model HDT
30 10, Copley Scientific Ltd., Nottingham, U.K.) was

1 used for testing diffusion of the substance across a
2 cell membrane.
3
4 Tablets from each batch were weighed and the
5 theoretical nicotine contents were calculated and
6 noted. The experimental membrane was secured tightly
7 to the cells, as show above. Single layer visking
8 dialysis membrane or porcine buccal mucosa was used
9 as the test membrane. Buccal mucosa was collected
10 and prepared. Porcine mucosa was used the same day as
11 the animal was sacrificed. The 5 mL cells were then
12 filled with distilled water from the solution
13 reservoir and the clamps secured. The cell stirrers
14 and the cell heater were switched on to heat the
15 solution to 37°C. To start, 100 µL of water was
16 placed on the upper side of the membrane and the
17 tablet was placed gently on the surface. 50 µL of
18 water was added to the tablet and membrane interface
19 at 30 minute intervals using an automatic pipette to
20 maintain adequate wetting of both the tablet and the
21 membrane. At certain time intervals, 5 mL samples
22 were withdrawn from the cells and the nicotine
23 content and hence the percentage nicotine released
24 from the tablet was investigated over a 4 hour period
25 using U.V. analysis. The dissolution runs were
26 repeated in triplicate for each batch. The area
27 available for drug permeation in to solution was
28 0.785 cm².
29
30 The results of the uniformity of weight experiment
31 are tabulated in table 4.1.

1 **Table 4.1.** Uniformity of weight for batches A - F
2 (n=10) .

Tablet	A	B	C	D	E	F
Mean Weight / mg	100.69	100.10	100.31	100.32	99.90	100.29
(RSD / %)	(0.732)	(0.309)	(0.268)	(0.387)	(0.293)	(0.394)

3 The expected weight of the tablets was 100 mg. All
4 tablet weights were 100 mg \pm 2 mg. The average
5 weight from 10 tablets in each batch was 100 mg \pm 1
6 mg. Additionally the variation in tablet weights
7 within each batch was very low as indicated by the
8 low percentage relative standard deviation values in
9 table 4.1. It can therefore be concluded that the
10 dry mixing and direct compression of the tablets
11 produces a uniform batch with regard to tablet
12 weight.

13
14 The NHT recovered during the assay is quoted as a
15 percentage of the theoretical NHT in the tablet (10 %
16 of tablet weight). The mean percentage NHT recovered
17 for each tablet batch is tabulated below in table
18 4.2.

19
20 **Table 4.2.** Uniformity of active ingredient for
21 batches A - F (n=3) .

Tablet	A	B	C	D	E	F
Mean NHT	98.74	98.60	100.15	97.66	96.70	95.78
recovered / %	(3.95)	(1.88)	(3.23)	(2.46)	(1.23)	(0.78)
(RSD / %)						

22
23 The assay results showed that not one tablet
24 contained greater or less than 5 % of the theoretical
25 nicotine content of the tablet. Combined with the

1 low deviation of tablet weights means that the
2 tablets contained $10 \text{ mg} \pm 0.5 \text{ mg}$ NHT. These results
3 fall well within the limits of 90 - 110% set out by
4 the British Pharmacopoeia. The low standard
5 deviations achieved again confirm that the method of
6 tablet manufacture is suitable for producing uniform
7 tablet batches.

8
9 The mean tablet crushing strengths are shown below in
10 table 4.3.

11
12 **Table 4.3.** Tablet crushing strength for batches A - F
13 (n=5).

Formulation	A	B	C	D	E	F
Mean crushing strength /	156.0	140.8	142.6	154.4	174.6	183.6
Newtons (RSD / %)	(5.82)	(10.52)	(8.31)	(4.16)	(3.05)	(0.98)

14
15 Few conclusions may be drawn from the data in table
16 4.3. Formulations A - D do not show marked
17 differences in crushing strength and combined with
18 the relatively large standard deviations firm
19 conclusions may not be drawn. Formulations E and F
20 with 40 % and 50 % HPC show slightly higher crushing
21 strengths than the other formulations, perhaps due to
22 the ability of HPC to act as a binding agent. There
23 are no recommendations for buccal release tablets and
24 as the tablets are designed to swell as opposed to
25 disintegrate and dissolve as with an oral tablet, the
26 higher values noted are perhaps appropriate.

27

1 The percentage weight loss of five tablets from each
2 batch after 5 minutes friability testing is tabulated
3 in table 4.4.

4
5 **Table 4.4.** Tablet friability results; Weight loss
6 from batches A - F.

Tablet	A	B	C	D	E	F
Weight loss / %	0.12	0.06	0.06	0.02	0.08	0

7
8 As discussed earlier, the friability tests are
9 designed to simulate conditions that may be
10 experienced by a tablet during production, packaging
11 and transportation. The weight loss from the tablets
12 has been demonstrated to be extremely low perhaps as
13 a function of the tablet hardness. These results
14 indicate that such a formulation would be resistant
15 to abrasion and therefore resistant to loss of tablet
16 weight including the loss of active ingredient
17 through normal processes until the product is used.

18
19 The water uptake profiles of formulations A- F are
20 shown in figure 6.

21
22 As can be clearly seen from figure 6, the swelling
23 profile formulation A is considerably greater than
24 observed for formulations B - F. Over the first 6
25 hours, formulation A has a more rapid weight increase
26 due to a greater uptake of water. The formulation
27 then continues to take up water over the 24 hour test
28 period resulting in a 175.5 % (± 2.55 % RSD) weight
29 increase compared with the dry tablet weight. This

1 larger and more rapid weight increase is due to the
2 absence of HPC from the formulation, which allows the
3 hydrophilic polymer carbopol to uptake the water in
4 to the buccal tablet. Figure 6 also indicates that
5 there is little or no difference between the swelling
6 profiles of formulations B - F, which contain between
7 10 and 50 % HPC. These formulations do not swell
8 to a great extent after the first 6 hours.
9 Formulation B gains an average of 13.5 % in weight
10 between 6 and 24 hours, formulations C - F gain
11 between 1.39 and 4.27 %, which suggests that the
12 formulations are approaching maximal swelling at
13 approximately 6 hours. The addition of HPC to the
14 formulation appears to counteract the strong swelling
15 properties of carbopol, this may be explained by the
16 hydrated matrix properties of HPC which controls the
17 penetration of water into the tablet. Concentrations
18 of 20 - 50 % HPC show no significant difference in
19 weight gain (swelling rate) between 6 - 24 hours.
20
21 The tablet dimensions measured over the 24 hour
22 period showed similar trends compared to the weight
23 increase. Despite large experimental standard
24 deviations (2.5 - 33 % RSD), due to the difficulty of
25 measuring a soft hydrated tablet, an increase in the
26 HPC concentration of the formulation resulted in a
27 smaller size increase of the tablet. The dimensions
28 of formulation A increased to a larger extent than
29 formulations B - F, which swelled to a comparable
30 extent. This may again be explained by the matrix
31 forming properties of HPC, which controls the uptake

of water by the formulation. The tablet size increase for formulations B - F between 6 and 24 hours is again very small, again suggesting that at 6 hours the tablets are approaching maximal swelling. The actual data is recorded in tables 4.5. and 4.6.

Table 4.5. Axial swelling of buccal bioadhesive tablets

Time / Hours	Axial size increase / %					
	A	B	C	D	E	F
0.5	11.92	14.70	9.36	12.16	14.76	5.28
1	17.02	20.57	13.10	23.83	26.19	9.72
2	28.84	28.43	29.00	32.71	34.76	10.28
3	33.99	30.39	29.95	35.03	34.29	14.45
4	38.54	30.88	36.45	36.91	35.72	17.39
6	47.13	32.84	38.35	37.38	40.48	20.82
24	60.23	43.14	35.08	37.38	37.14	27.20

Table 4.6. Radial swelling of buccal bioadhesive tablets

Time / Hours	Radial size increase / %					
	A	B	C	D	E	F
0.5	14.17	11.11	14.44	11.39	13.89	6.32
1	15.56	13.33	15.00	15.00	15.28	13.56
2	23.33	19.45	18.89	22.67	17.50	19.37
3	28.89	20.56	22.22	21.39	17.50	20.34
4	32.50	25.56	27.78	26.39	17.22	28.05
6	37.78	26.11	32.22	27.78	22.78	27.60
24	60.00	35.28	32.78	30.83	28.61	27.62

One theoretical model of mucoadhesion suggests that 3 stages are involved, namely; intimate contact, interpenetration of mucus / polymer macromolecules and formation of secondary non-covalent bonds. Intimate contact between the mucoadhesive and the

1 mucus requires the swelling and spreading of the
2 bioadhesive material to result in a close or intimate
3 contact. The axial tablet dimension, which would be
4 in contact with the mucosal membrane, swells on
5 average by 11.3 % in 30 minutes and should be
6 sufficient to produce the intimate contact required
7 for mucoadhesion.

8
9 The swelling study may also be of importance when
10 assessing the dissolution behaviour of these
11 formulations. HPC, a semi-synthetic polymeric
12 derivative of cellulose, will swell in an aqueous
13 medium to form a gel-like matrix that controls
14 release by acting as a barrier to drug dissolution
15 and diffusion. The HPC gel acts as a physical barrier
16 through which the dissolution medium must penetrate
17 to dissolve the drug, the drug solution must then
18 again penetrate the gel to be available for
19 absorption. Carbopol on the other hand is
20 hydrophilic and will swell faster and to a greater
21 extent, promoting the penetration of the dissolution
22 medium into the tablet matrix. The alteration of
23 polymer content of the matrix will alter the drug
24 release rate. Formulation A containing no HPC should
25 allow the dissolution medium to penetrate the tablet,
26 dissolve the drug and diffuse out of the tablet,
27 resulting in rapid drug release. Formulations B - F
28 containing increasing HPC content should retard drug
29 release by forming the gel barrier resulting in
30 controlled drug release over a number of hours. Due
31 to the small differences in swelling of formulations

1 B - F, it is not possible to predict any differences
2 with regard to drug dissolution.

3

4 Nicotine release profiles for formulations A - F are
5 shown in figure 7.

6 From figure 7 it can be seen that only approximately
7 50 - 60 % drug release was achieved from the
8 formulations. HPC was expected to control the
9 release in such a manner over the 4 hour period, it
10 is therefore surprising that formulation A containing
11 no HPC released only 60 % of NHT in this time.

12

13 The dissolution data was investigated using equation
14 1 as defined above (Peppas and Sahlin, 1989). The
15 data from these plots are presented in table 4.8.

16

17 The calculated n value allows the release mechanism
18 from a cylindrical system such as a tablet to be
19 characterised according to table 4.7. (Peppas and
20 Sahlin 1989).

21

22 **Table 4.7.** Diffusion exponent and solute release
23 mechanism

<i>Diffusion exponent (n) from a cylinder</i>	<i>Release mechanism</i>
0.45	Fickian Diffusion
0.45 < n < 0.89	Anomalous transport
0.89	Case II transport

24

25 Fickian diffusion describes t^{-2} kinetics and case II
26 transport describes constant zero order drug release.
27 Polymer swelling and drug diffusion through a matrix

do not normally follow Fickian release behaviour, due to the existence of a molecular relaxation process (Vigoreaux and Ghaly 1994 Drug Development and Industrial Pharmacy 20(16) 2519-2526). This type of drug release results in intermediate values for n and is classed as anomalous (non Fickian) transport.

Table 4.8. Diffusional exponents (n) and kinetic constants (k) for NHT dissolution from buccal adhesive nicotine tablets ($n=3$).

Formulation	Diffusional exponent (n) (RSD / %)	Kinetic constant / hr^{-1} (k) (RSD / %)	r^2 (RSD / %)	Release mechanism
A	0.6857 (12.05)	0.2520 (14.07)	0.974 (0.27)	Anomalous transport
B	0.7200 (6.75)	0.2174 (7.20)	0.987 (0.59)	Anomalous transport
C	0.8413 (2.83)	0.1940 (4.19)	0.982 (0.84)	Anomalous transport
D	0.8341 (5.31)	0.1855 (0.22)	0.994 (0.73)	Anomalous transport
E	0.7778 (9.26)	0.1905 (3.85)	0.976 (1.40)	Anomalous transport
F	0.7768 (9.78)	0.1915 (8.71)	0.983 (0.357)	Anomalous transport

The n value for formulation A is almost exactly mid range for anomalous non-Fickian release mechanism. However, the n value increases in the other formulations that contain HPC. Formulations C and D containing 20 and 30 % HPC respectively show n values approaching case II transport i.e. zero order NHT release. For formulations E and F containing 40 and

1 50 % HPC, the n values appear to tail off. This
2 suggests the most appropriate matrix for NHT release
3 contains around 20 - 30 % HPC providing release
4 approaching zero order. The variation of the
5 diffusional exponent (n) with HPC is summarised in
6 figure 8.

7
8 The kinetic rate constants (k) in table 4.8
9 incorporate the structural and geometrical
10 characteristics of the release device and may be used
11 to compare formulations. Formulation A, containing
12 no HPC exhibits the greatest rate constant (k). The
13 addition of HPC, as a matrix former results in a
14 decrease in the rate constant as the hydrated HPC
15 provides a barrier to drug dissolution. The rate
16 decreases to a minimum at 30 % and remains relatively
17 constant with increasing HPC concentration. The
18 variation in kinetic rate constant with HPC content
19 is shown graphically in figure 9.

20

21 NHT dissolution using the diffusion dissolution
22 method followed zero order release kinetics using the
23 dialysis visking tubing as the model membrane. The
24 dissolution statistics are presented in table 4.9.

1 **Table 4.9.** NHT release rates from nicotine buccal
2 adhesive tablets (n=3)

Formulation	Release rate / %hr ⁻¹	(RSD / %)	r ²	(RSD / %)
A	4.4969	(2.41)	0.989	(0.58)
B	3.9375	(3.42)	0.938	(4.23)
C	3.4169	(2.66)	0.983	(0.53)
D	2.7309	(9.54)	0.983	(0.52)
E	2.8778	(7.91)	0.984	(1.45)
F	2.6863	(16.02)	0.994	(0.34)

3
4 Zero order case II transport was confirmed by
5 analysis of the dissolution data using equation 1 as
6 described above. Diffusion exponent (n) values were
7 between 0.89 and 1.45 in all formulations except
8 formulation B (n = 0.75). The lower correlation
9 value and larger RSD value for formulation B in table
10 4.9. may explain this.

11
12 The release rates quoted in table 4.9. again appear
13 to decrease with increasing HPC concentration. This
14 decrease in release rate appears to be linear to a
15 concentration of 30 % as can be seen in figure 10.

16
17 HPC contents of 30 % and above (formulations D, E and
18 F) produce NHT release rates that are not
19 significantly different (p > 0.05). This agrees with
20 the trend shown by the NHT release for the flow
21 through dissolution method and suggests that HPC
22 concentrations of above 30 % are not necessary to
23 produce a sustained release matrix for NHT.

24 It is worth noting that the release rates across the
25 dialysis visking tubing for formulation A are not
26 significantly different from the permeation rates of

1 nicotine from solution through the same membrane seen
2 in section 3.3.4.1. This suggests that limiting
3 factor to drug dissolution using this method is in
4 fact permeation across the membrane resulting in zero
5 order kinetics. When HPC is present in the
6 formulation, however, these rates decrease further.
7 Over the 4 hours, a maximum of 17 % NHT was released,
8 this decreased to 11.5 % for formulation F. When
9 compared with the results from the flow through
10 dissolution (50 - 60 %) this value is low, but may be
11 due to the nature of the membrane.

12
13 The diffusion dissolution apparatus was set up using
14 porcine buccal membrane. Due to the limited supply
15 of porcine mucosa, this experiment was carried out
16 once with formulation A. Using HPLC detection, only
17 1.4 % of the NHT content of the tablet was recovered
18 in the receptor solution after 4 hours. This figure
19 is very low compared with the artificial membrane and
20 may be due to the thickness of the membrane and
21 problems of using animal tissue. The experiment was
22 repeated using formulation A and fresh porcine
23 mucosa, however instead of sampling from the receptor
24 solution, after 4 hours that tablet was assayed to
25 determine the NHT remaining in the formulation.
26 Following this method, the HPLC tablet assay detected
27 6.95 mg of NHT remaining, which was calculated to be
28 69 % of the NHT content of the tablet. It could
29 therefore be concluded that 31 % of the available NHT
30 (3.11 mg) had been released from the tablet. All the
31 NHT release was not able to cross the porcine

1 membrane and enter the receptor solution, most likely
2 due to the 2 mm thickness of the membrane (the upper
3 200 μm is known to be the barrier to buccal
4 permeation) and the small orifice (0.785 cm^2)
5 available for the NHT to enter the receptor solution.
6 From this data it is suggested that the NHT has been
7 released from the formulation and partitioned into
8 the buccal tissue; however due to the reasons
9 mentioned above, the NHT remained in the tissue and
10 was not passed into the receptor solution.

11

12 All bilayer tablets weighed $150 \text{ mg} \pm 3 \text{ mg}$. The
13 average weights of 3 tablets from all batches ranged
14 from 149.0 mg to 150.5 mg with a corresponding
15 percentage relative standard deviation value of 0.17
16 % to 1.19 %. These results suggest that the method
17 of preparation is suitable in producing bilayer
18 tablets of uniform weight.

19

20 Two formulations were selected in the determination
21 of active ingredient content, formulation CRL B + RRL
22 2 mg and formulation CRL D + RRL 5 mg. The NHT
23 recovered during the assay is quoted as a percentage
24 of the theoretical NHT in the tablet.

25

26 **Table 4.10.** Uniformity of active content for two
27 bilayer tablet formulations (n=3).

CRL	RRL	Mean NHT recovered / %	RSD / %
A	2	98.52	1.73
D	5	98.88	1.08

28

1 All of the tablets assayed contained 100 % \pm 2.5 % of
2 the theoretical NHT content. This, combined with the
3 low deviations quoted in table 4.10 again suggests
4 that the method of manufacture of the bilayer tablets
5 is suitable for producing a tablet of uniform active
6 content.

7 One bilayer tablet formulation was selected to carry
8 out the crushing strength determination using the
9 method outlined for formulations A - F. The mean
10 crushing strength (n=5) for formulation CRL B + RRL 2
11 mg was 167.4 N (5.08 % RSD). This value is
12 significantly higher ($p < 0.05$) than the formulation
13 B controlled release monolayer alone. This is
14 probably due to the double compression cycle of the
15 bilayer tablet resulting in a harder tablet.

16

17 Formulation CRL B + RRL 2 mg was again used for the
18 friability determination using the method outline for
19 formulations A - F. During the 5 minute friability
20 test, 5 tablets lost 0.15 % of their combined weight.
21 This is higher than the 0.06 % for formulation B
22 controlled release monolayers alone, however this
23 value is still low. The two layers remained joined
24 and intact after the 5 minute test. This suggests
25 that the bilayer tablets would be resistant to
26 abrasion and therefore resistant to loss of tablet
27 weight, including the loss of active ingredient,
28 through normal processes until the product is used.

29

30 NHT release from the bilayer tablets was analysed
31 using the flow through dissolution method outlined

1 above. Release profiles for bilayer tablets
2 containing controlled release layers A and E are
3 shown in figures 11 and 12. These profiles are
4 representative of the trends seen in the release
5 behaviour of all bilayer tablets.

6
7 Figures 11 and 12 show that the bilayer tablets
8 produce a biphasic drug release profile, with a more
9 rapid release of nicotine over the first hour of
10 dissolution testing. Additionally, the rate of drug
11 release from the bilayer tablet with the 5 mg RRL was
12 greater than that from the bilayer tablet containing
13 the 2 mg RRL. This trend was seen in all bilayer
14 tablet batches produced. The bilayer tablets
15 containing the 2 mg RRL released all the NHT content
16 in, on average 26.25 minutes, ranging from 25 to 30
17 minutes (n=18). The 5 mg RRL released all the NHT in,
18 on average 43.3 minutes, ranging from 40 - 47.5
19 minutes (n=18).

20
21 After 1 hour, the drug release profiles level out and
22 appear parallel to tablets containing no RRL. This
23 trend was confirmed by analysis of the dissolution
24 data from 1 to 3 hour time period. There was no
25 significant difference ($p > 0.05$, $n=3$) in the
26 gradients of the lines (release rates) over this time
27 scale for the CRL alone, the CRL and 2 mg RRL and the
28 RRL and 5mg RRL bilayer tablets. This confirmed that
29 after one hour, release rates were governed by the
30 CRL alone with no contribution by the RRL.

31

1 To determine the NHT release profile of the RRL over
2 the first hour of dissolution testing, bilayer
3 tablets containing CRL A and CRL B with the 2 mg RRL
4 were subjected to flow through dissolution over one
5 hour with more frequent sampling times. The NHT
6 release profiles are shown in figure 4.10.

7
8 Figure 4.10. indicates that the NHT release from
9 bilayer tablets over the first hour followed zero
10 order release kinetics. The time taken for the
11 bilayer tablet to release the 2 mg NHT was 27.78
12 minutes (8.44 % RSD). This compares favourably to
13 the 26.35 minutes identified above. Due to the
14 agreement in results, the one hour dissolution
15 experiment was not repeated with the 5 mg RRL.

16
17 Dissolution data was again analysed using equation 1.
18 The results are presented in table 4.11.

19
20 **Table 4.11.** Diffusional exponents (n) and kinetic
21 constants (k) for NHT dissolution from buccal
22 adhesive nicotine tablets (n=3).

1

CRL	RRL	Diffusional Exponent (n) (RSD / %)	Kinetic Constant / hr^{-1} (k) (RSD / %)	r^2 (RSD / %)	Release Mechanism
A	-	0.6857 (12.05)	0.2520 (14.07)	0.974 (0.27)	Anomalous transport
A	2	0.6383 (19.10)	0.3341 (11.55)	0.965 (0.79)	Anomalous transport
A	5	0.5926 (9.86)	0.3717 (4.51)	0.946 (0.65)	Anomalous transport
B	-	0.7200 (6.75)	0.2174 (7.20)	0.987 (0.59)	Anomalous transport
B	2	0.5882 (20.71)	0.3426 (13.74)	0.962 (1.14)	Anomalous transport
B	5	0.4961 (3.57)	0.3896 (6.02)	0.929 (1.59)	Anomalous transport
C	-	0.8413 (2.83)	0.1940 (4.19)	0.982 (0.84)	Anomalous transport
C	2	0.6020 (13.94)	0.3444 (8.33)	0.970 (2.06)	Anomalous transport
C	5	0.4853 (6.80)	0.4154 (6.26)	0.932 (2.02)	Anomalous transport
D	-	0.8341 (5.31)	0.1855 (0.22)	0.994 (0.73)	Anomalous transport
D	2	0.7075 (3.23)	0.2894 (5.52)	0.956 (1.05)	Anomalous transport
D	5	0.4695 (26.60)	0.4128 (12.84)	0.962 (2.08)	Anomalous transport
E	-	0.7778 (9.26)	0.1904 (3.85)	0.976 (1.40)	Anomalous transport
E	2	0.5639 (12.77)	0.3402 (7.35)	0.988 (0.91)	Anomalous transport
E	5	0.5023 (8.00)	0.4066 (2.46)	0.945 (1.06)	Anomalous transport
F	-	0.7768 (9.78)	0.1915 (8.71)	0.983 (0.983)	Anomalous transport
F	2	0.5892 (20.00)	0.3024 (8.57)	0.938 (3.27)	Anomalous transport
F	5	0.4823 (10.21)	0.3588 (8.36)	0.921 (4.35)	Anomalous transport

1 The calculated n values are all within the range
2 indicating anomalous non-Fickian release mechanism.
3 However table 4.11. indicates that the n values for
4 the bilayer tablets containing 5 mg RRL are lower
5 than for the bilayer tablet containing the 2 mg RRL
6 and both are lower than the CRL monolayers alone.
7 The n values for the monolayers, as discussed '
8 earlier, approached zero order release. The addition
9 of the 5 mg RRL results in this value decreasing and
10 the mechanism of release, although still anomalous
11 transport, now approaches Fickian type release where
12 drug release occurs by diffusion of the drug due to a
13 chemical potential gradient. The departure from zero
14 order release may be explained by the distinct
15 biphasic release profiles identified above, where
16 rapid release from the RRL occurs over the first
17 hour, followed by NHT release approaching zero order
18 kinetics over the remaining 3 hours.
19
20 Modifications and improvements can be incorporated
21 without departing from the scope of the invention.
22 For example in many embodiments the tablet can
23 include a sugar such as mannitol, sucrose or glucose
24 that can contain the substance to be released within
25 the tablet and can also improve the taste of the
26 tablet in the mouth. Any sugar can be suitable for
27 this purpose.

1 Claims

2

3 1. A method of delivering a substance to the
4 buccal mucosa of a subject, the method
5 comprising providing a tablet comprising a
6 quantity of the substance to be delivered, the
7 tablet having multi-phasic release properties
8 to release controlled amounts of the substance
9 to the subject over time, and releasing the
10 substance from the tablet in the subject's
11 mouth.

12

13 2. A method as claimed in claim 1, wherein the
14 tablet has a multi-portion structure and
15 different amounts of substance are released
16 from each portion.

17

18 3. A method as claimed in claim 1 or claim 2,
19 wherein the tablet has a multi-portion
20 structure and the different portions release
21 substance at different rates.

22

23 4. A method as claimed in any preceding claim,
24 wherein the tablet is attached to the buccal
25 mucosa by a bioadhesive.

26

27 5. A method as claimed in claim 4, wherein the
28 bioadhesive comprises one or more of carbopol,
29 chitosan, hydroxypropyl cellulose, sodium
30 carboxymethyl cellulose, hydroxypropylmethyl
31 cellulose.

- 1 6. A method as claimed in claim 4 or claim 5,
2 wherein the bioadhesive is disposed in a
3 localised portion of the tablet.
4
- 5 7. A method as claimed in any preceding claim,
6 wherein the tablet contains agents to control
7 the release of the substance.
- 8 8. A method as claimed in claim 7, wherein the
9 release-controlling agents comprise one or more
10 of hydroxypropylmethyl cellulose, hydroxypropyl
11 cellulose, poly D L lactide- and glycolide-
12 related polymers.
13
- 14 9. A method as claimed in any preceding claim,
15 wherein a portion of the tablet releases a
16 quantity of the substance quickly to satisfy a
17 craving in the subject for addictive
18 substances.
19
- 20 10. A method as claimed in any preceding claim,
21 wherein the substance comprises one or more of
22 nicotine, cannabinoids, antibiotics, analgesics
23 and anaesthetics.
24
- 25 11. A method as claimed in any preceding claim,
26 wherein the substance is provided in a
27 localised portion having a coating that
28 exhibits the desired release characteristics.
29
- 30 12. A method as claimed in any preceding claim,
31 wherein the tablet is a multi-layer tablet and

1 the layers have different release
2 characteristics.

3

4 13. A method as claimed in claim 12, wherein an
5 outer layer releases substance at a faster
6 rate than an inner layer.

7

8 14. A method as claimed in any preceding claim,
9 wherein the tablet formulation comprises a
10 controlled release layer containing a
11 bioadhesive for attachment to the buccal mucosa
12 and release of substance at a constant rate,
13 and a rapid release layer for rapid release of
14 substance into the systemic circulation through
15 the oral mucosa.

16

17 15. A method as claimed in any preceding claim,
18 wherein the tablet comprises concentric layers.

19

20 16. A method as claimed in any one of claims 1-14,
21 wherein the tablet has two (or more) flat
22 layers in a sandwich structure.

23

24 17. A tablet for delivery of a substance to the
25 buccal mucosa of a subject, the tablet
26 comprising a quantity of substance to be
27 delivered to the subject, the tablet having
28 multi-phasic release properties adapted to
29 release controlled amounts of the substance to
30 the subject over time.

31

- 1 18. A tablet according to claim 17, having a multi-
2 portion structure with different rates of
3 release of substance associated with each
4 portion.
5
- 6 19. A tablet according to claim 18, having
7 different homogeneous portions with different
8 release characteristics.
9
- 10 20. A tablet according to claim 18 or claim 19,
11 having different quantities of substance
12 associated with respective portions.
13
- 14 21. A tablet according to any one of claims 18-20,
15 wherein an inner portion is adapted for slower
16 release of substance than an outer portion.
17
- 18 22. A tablet according to any one of claims 18-21,
19 wherein the outer portion of the tablet is
20 adapted to release a quantity of the substance
21 quickly.
22
- 23 23. A tablet according to any one of claims 18-22,
24 wherein the respective portions contain a
25 homogeneous dispersion of the substance
26 throughout each portion.
27
- 28 24. A tablet according to any one of claims 18-23,
29 wherein the substance is provided in a discrete
30 portion having a coating that exhibits the
31 desired release characteristics.

- 1 25. A tablet according to any one of claims 17-24
2 wherein the tablet has a multi-layer structure.
3
- 4 26. A tablet according to claim 25, wherein the
5 layers of the tablet are concentric.
6
- 7 27. A tablet according to claim 25, wherein the
8 tablet has two or more flat layers in a
9 sandwich structure.
10
- 11 28. A tablet according to any one of claims 17-27,
12 comprising a bioadhesive.
13
- 14 29. A tablet according to any one of claims 17-28,
15 having a controlled release layer containing a
16 bioadhesive for attachment to the buccal mucosa
17 and sustained release of the substance at a
18 relatively constant rate, and a rapid release
19 layer for rapid release of the substance upon
20 contact with saliva in the mouth.
21
- 22 30. A tablet according to claim 28 or 29, wherein
23 the bioadhesive is in a localised portion of
24 the tablet.
25
- 26 31. A tablet according to any one of claims 28-30,
27 wherein the bioadhesive comprises one or more
28 of carbopol, chitosan, hydroxypropyl cellulose,
29 sodium carboxymethyl cellulose,
30 hydroxypropylmethyl cellulose.
31

- 1 32. A tablet according to any one of claims 17-31,
2 containing agents to control the release of the
3 substance.
4
- 5 33. A tablet according to claim 32, wherein the
6 agent comprises one or more of
7 hydroxypropylmethyl cellulose, hydroxypropyl
8 cellulose, poly D L lactide- and glycolide-
9 related polymers.
10
- 11 34. A tablet according to any one of claims 17-33,
12 wherein the substance is nicotine.
13
- 14 35. A tablet according to any one of claims 17-33,
15 wherein the substance comprises one or more of
16 cannabinoids, antibiotics, analgesics and
17 anaesthetics, and drugs for buccal infections.
18
- 19 36. A homogeneous tablet according to claim 18.

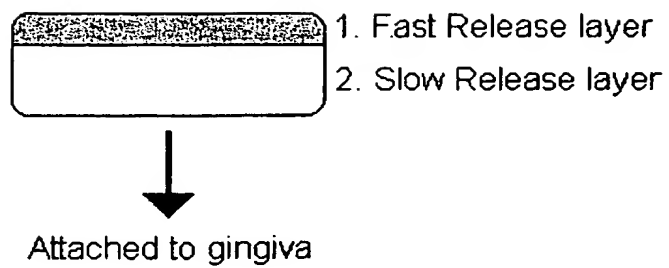
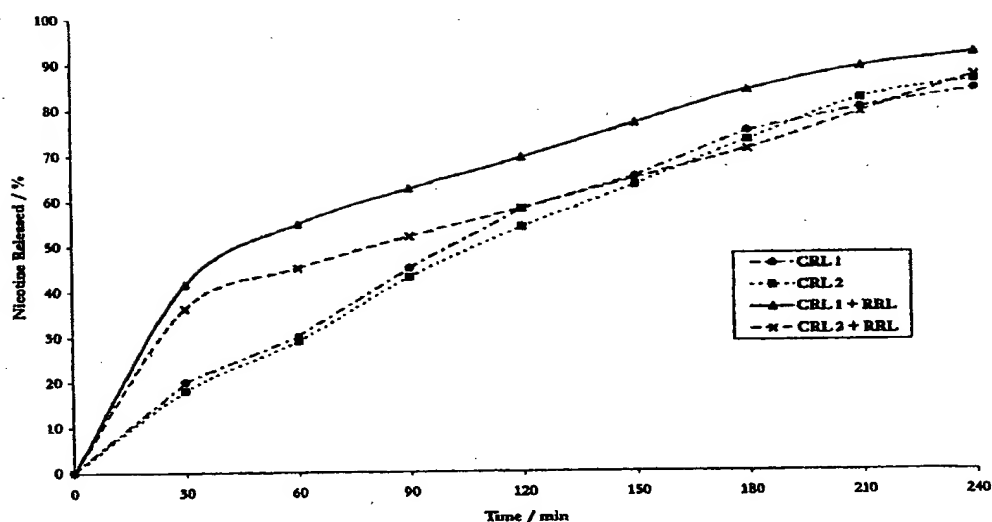


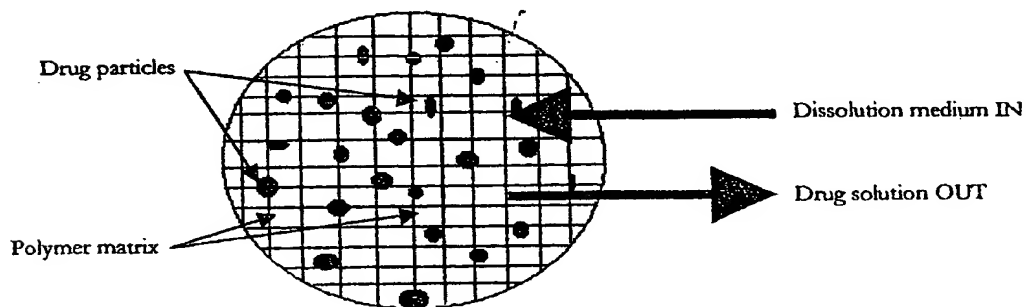
Figure 1.

FIG 2



Representative nicotine release profiles from the buccal bioadhesive formulations produced in this study.

FIG 3



Diagrammatic representation drug release from a polymer matrix.

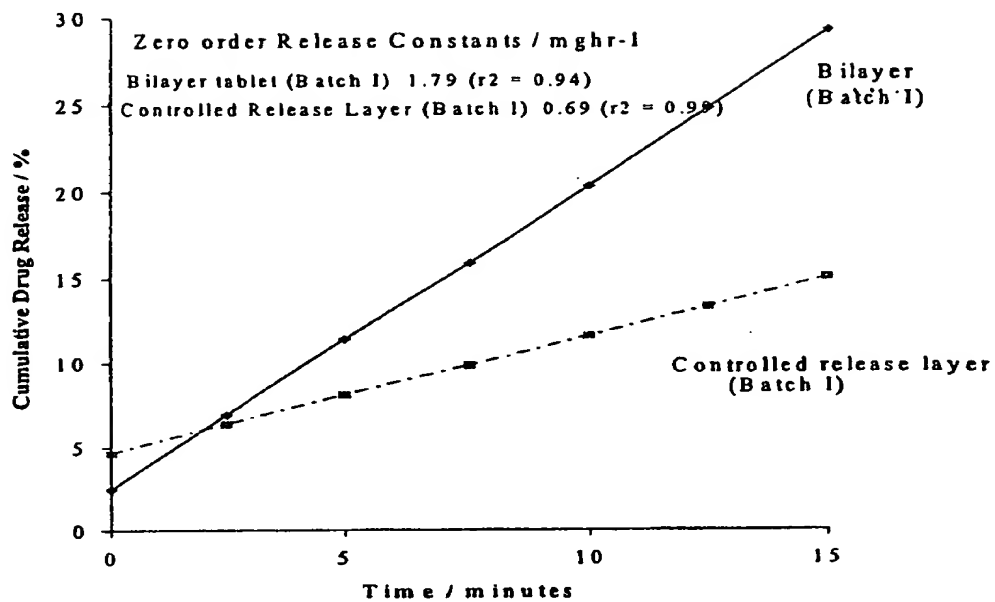


fig 1

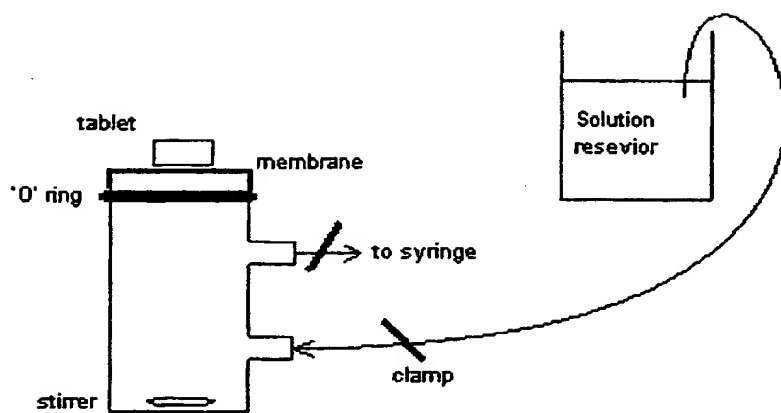


Figure 5. Diffusion dissolution apparatus

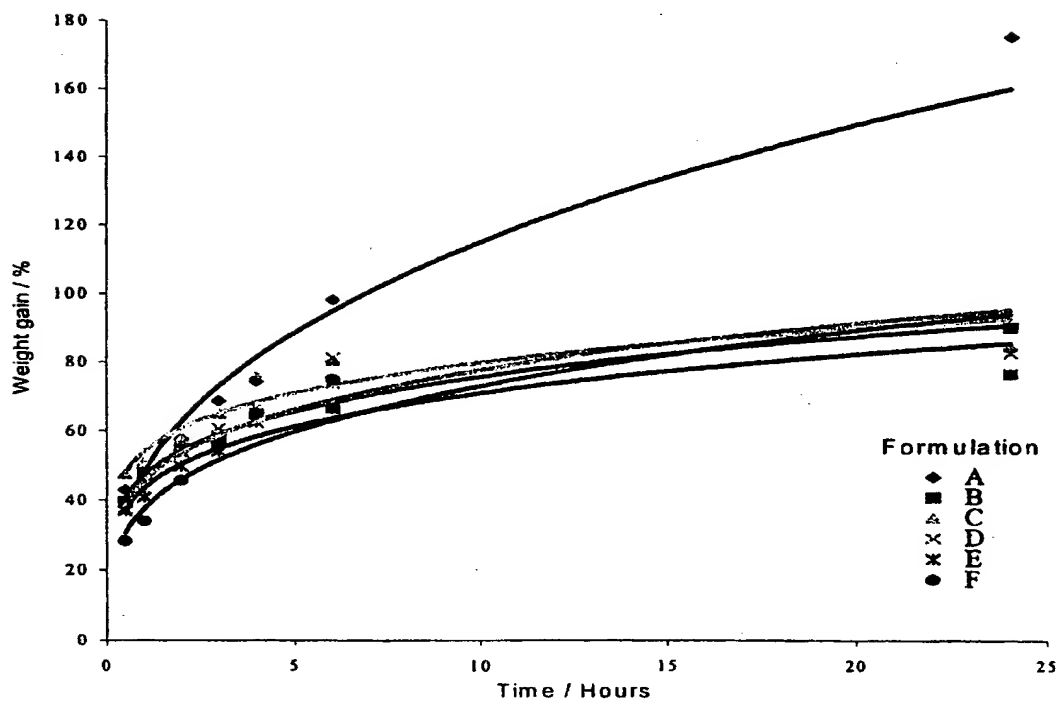


Figure 6. Water uptake profiles for buccal adhesive tablet batches A - F (n=3).

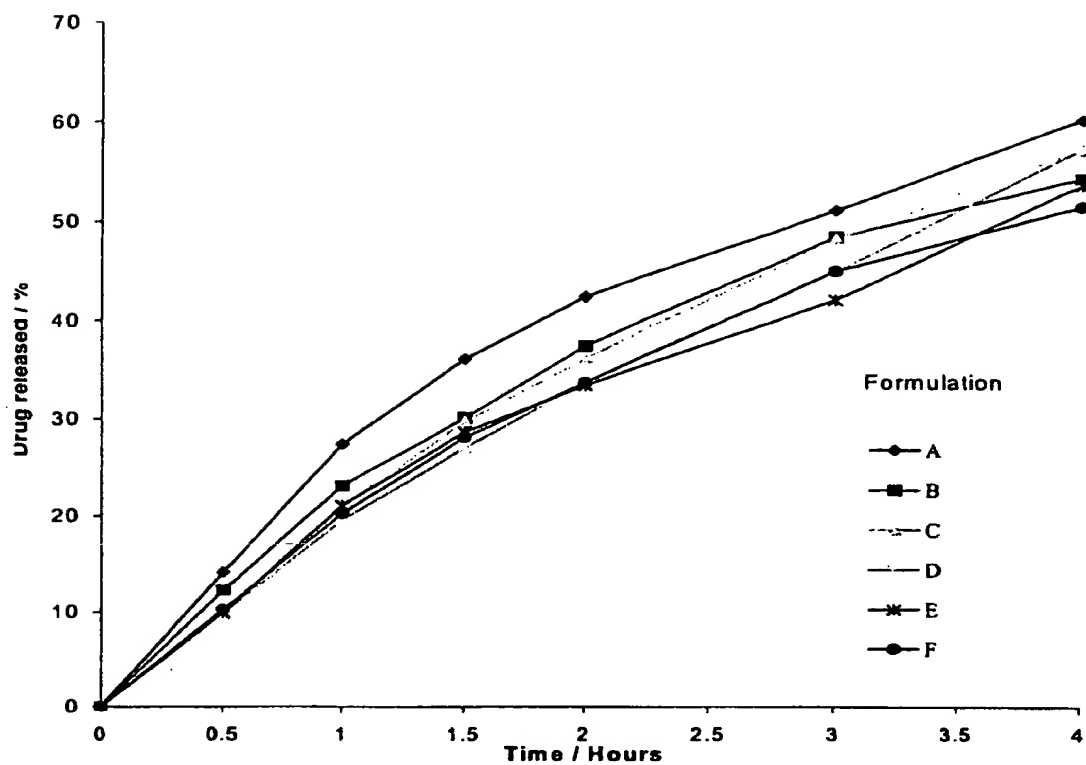


Figure 7. NHT dissolution profiles for buccal adhesive formulations A - F.

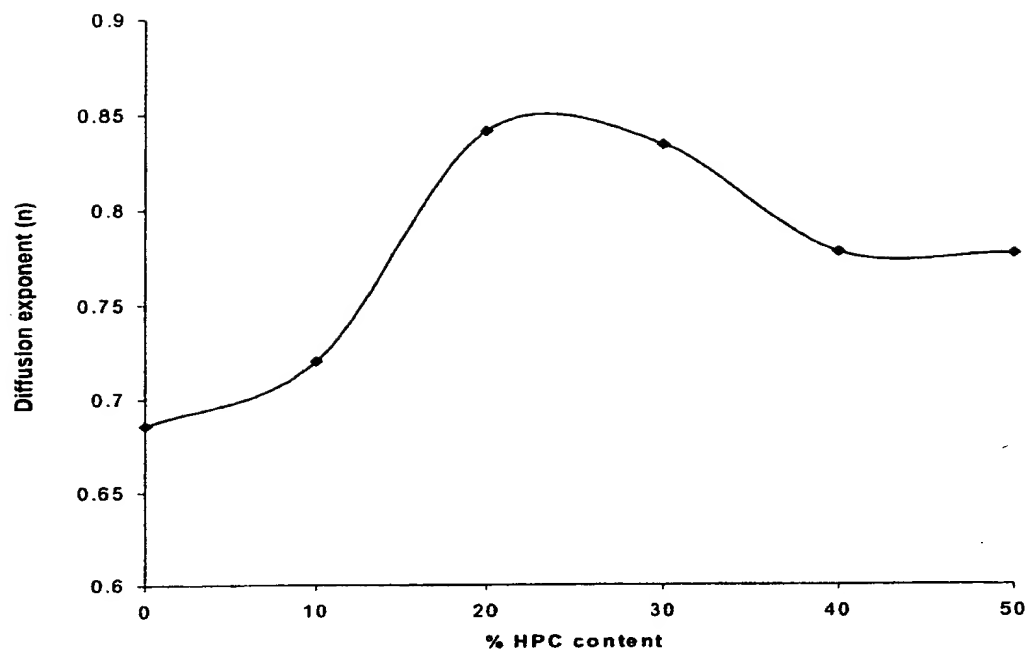


Figure 8. Diffusional exponent (n) values for nicotine buccal adhesive tablets

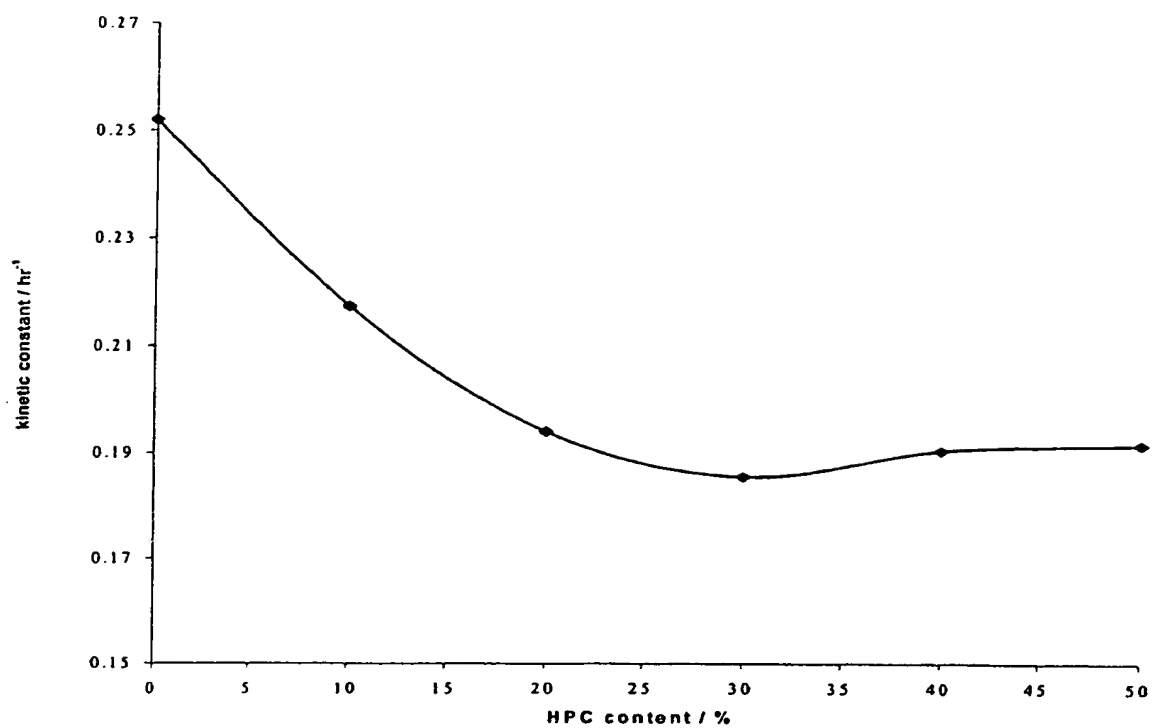


Figure 9. NHT kinetic rate constant values (k) for nicotine buccal adhesive tablets

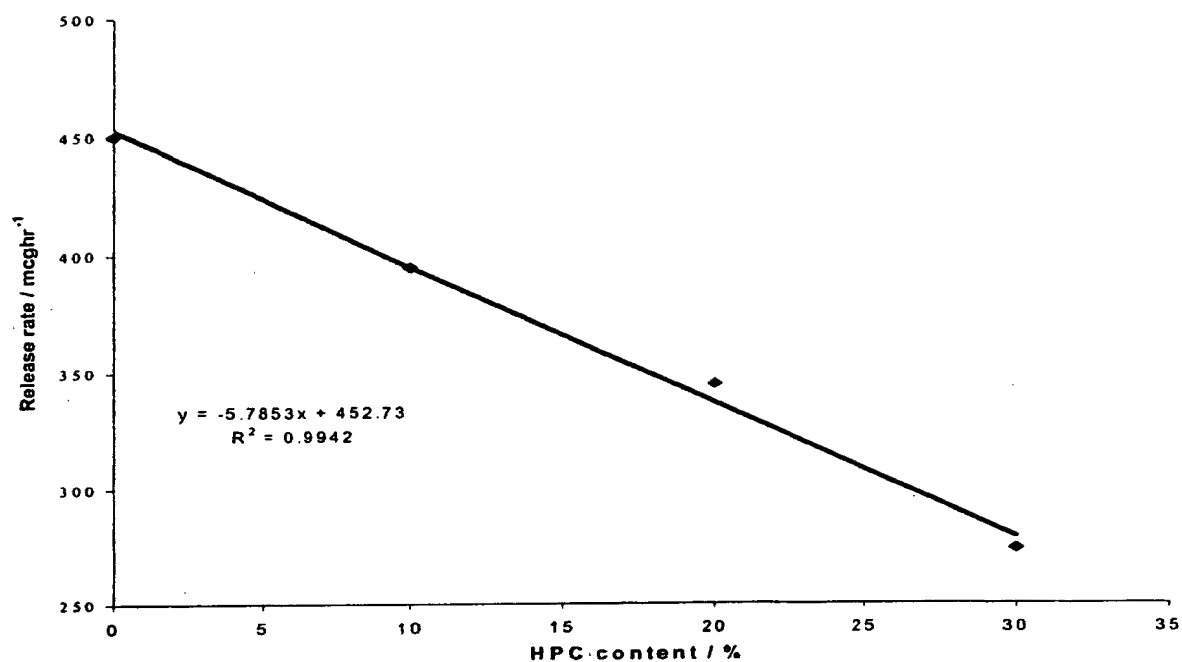
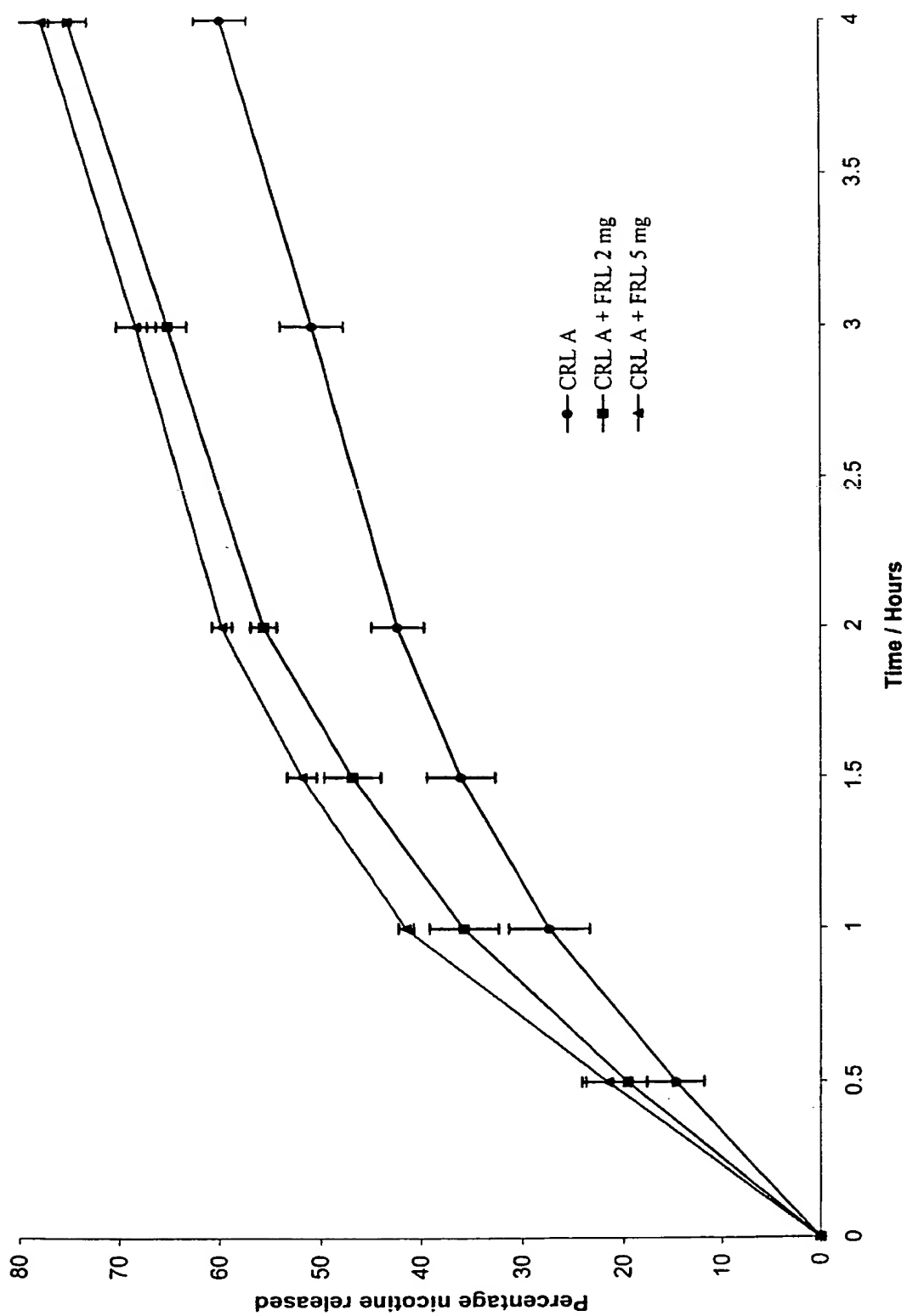


Figure 10. Demonstration of the linear relationship between NHT release rates and HPC content of nicotine buccal adhesive tablets using diffusion dissolution apparatus.

Fig 11

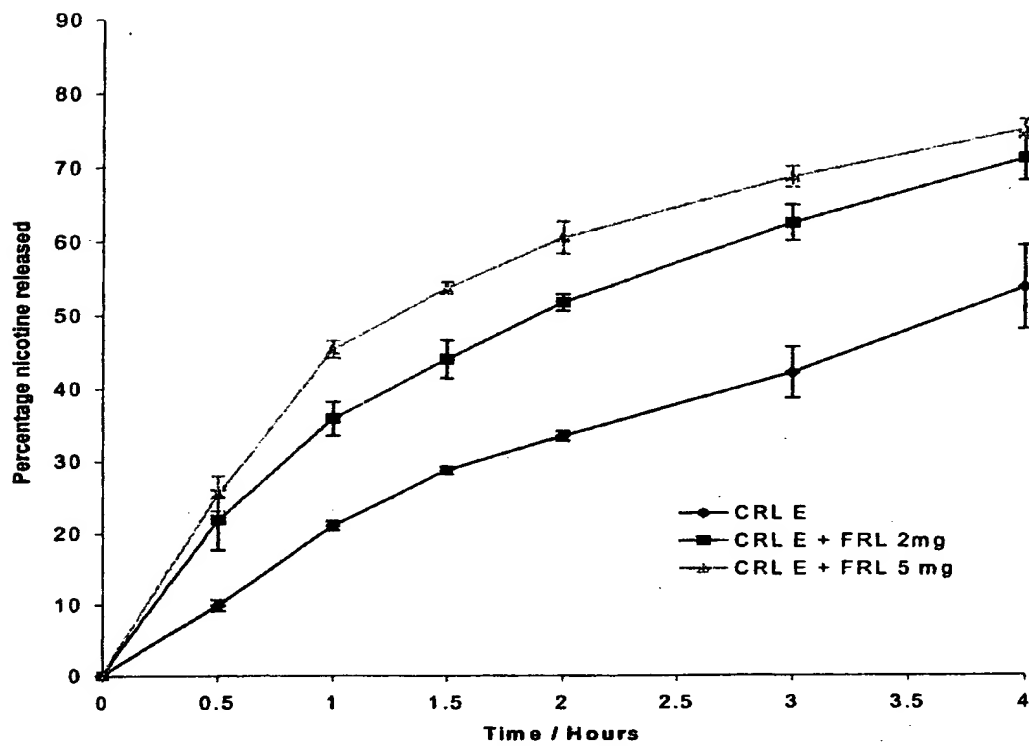


Figure 12. Dissolution profiles for formulation E and bilayer tablets consisting of formulation E and 2 mg and 5mg NHT fast release layers.

Figure 13. Drug release profiles of NHT bilayer tablets over the first hour of a 4 hour flow through dissolution test.

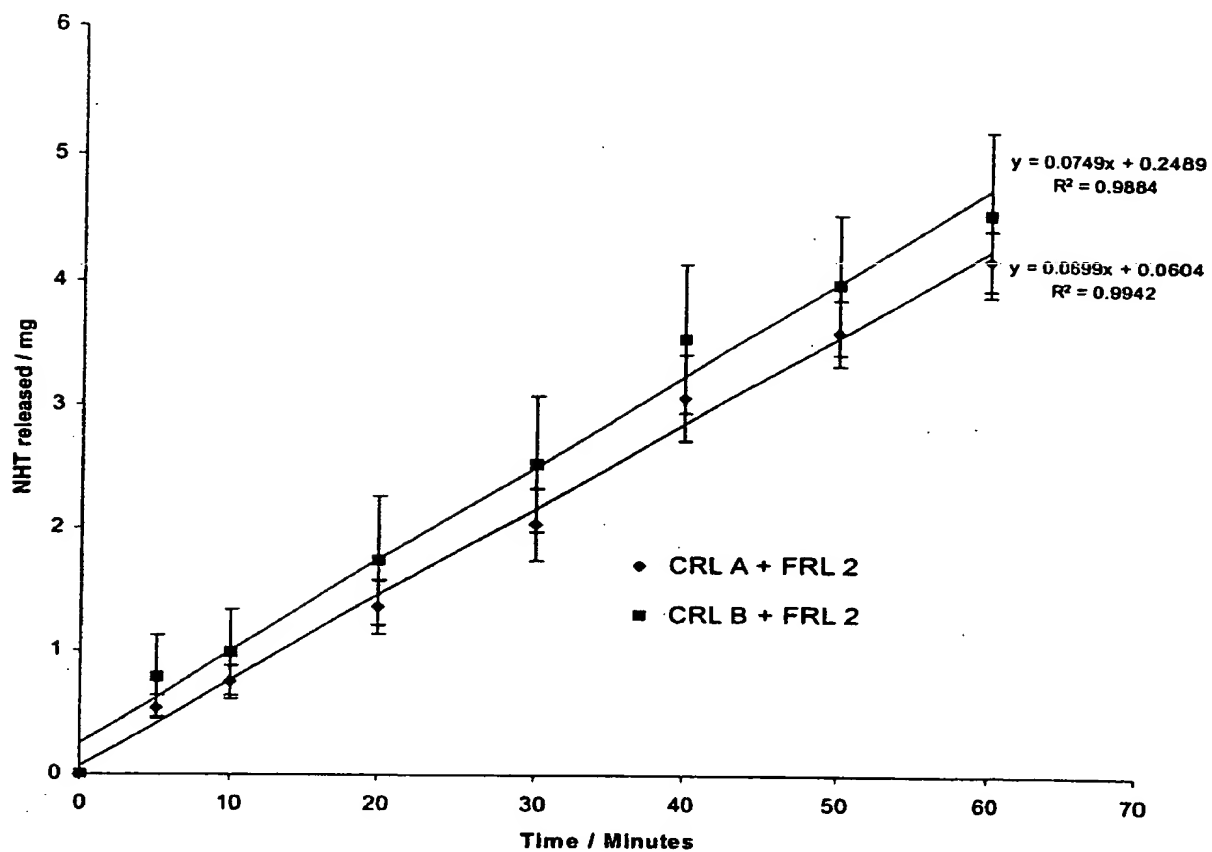


fig 13

INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 00/04428

A. CLASSIFICATION OF SUBJECT MATTER IPC 7 A61K9/24 A61K31/465		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) IPC 7 A61K		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 879 710 A (BROMET NORBERT E) 9 March 1999 (1999-03-09) column 1, line 12 - line 21 column 3, line 58 - column 4, line 2 column 4, line 33 - line 37 column 4, line 50 - column 5, line 5; claims 1,2,6; example 1; tables 1,2 <div style="text-align: center;">--- -/--</div>	1-8, 12-14, 16-23, 25, 27-33,36
<div style="display: flex; justify-content: space-between;"> <input checked="" type="checkbox"/> Further documents are listed in the continuation of box C. <input checked="" type="checkbox"/> Patent family members are listed in annex. </div>		
* Special categories of cited documents :		
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Date of the actual completion of the international search <div style="text-align: center;">27 February 2001</div>		Date of mailing of the international search report <div style="text-align: center;">12/03/2001</div>
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer <div style="text-align: center;">Marttin, E</div>

INTERNATIONAL SEARCH REPORT

national Application No

PCT/GB 00/04428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LEE Y ET AL: "Oral mucosa controlled delivery of LHRH by bilayer mucoadhesive polymer systems" JOURNAL OF CONTROLLED RELEASE, NL, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 37, no. 3, 1 December 1995 (1995-12-01), pages 251-261, XP004037428 ISSN: 0168-3659 page 252, left-hand column, line 4 - line 31 page 252, right-hand column, last paragraph; table 1 page 253, right-hand column, last paragraph -page 254, left-hand column, paragraph 1 page 254, left-hand column, last paragraph -page 255, right-hand column, paragraph 1; figure 2 page 260, line R, paragraph 2</p>	<p>1-7, 10, 12-14, 16-23, 25, 27-32, 35, 36</p>
X	<p>US 5 236 713 A (WATO TAKAHIKO ET AL) 17 August 1993 (1993-08-17)</p> <p>column 2, line 18 - line 24 column 2, line 34 - line 48 column 3, line 13 - line 41 column 3, line 54 - line 59 column 3, line 37 -column 4, line 25; claims; examples</p>	<p>1-8, 12-14, 16-23, 25, 27-33, 36</p>
X	<p>WO 98 46235 A (FIERUS MONIKA ;NEUSER DIETER (DE); BAYER AG (DE); WIEHL WOLFGANG) () 22 October 1998 (1998-10-22)</p> <p>page 1, paragraph 1 page 1, paragraph 3 - paragraph 4 page 3, last paragraph -page 4, paragraph 1; claims; examples</p>	<p>1-3, 10-13, 15, 17-19, 21, 24-26, 35, 36</p>
A	<p>WO 92 01445 A (ALZA CORP) 6 February 1992 (1992-02-06) page 5, paragraph 1 - paragraph 4 page 5, last paragraph -page 6, paragraph 2 page 6, last paragraph -page 7, line 1; claims 1, 2, 9, 12, 13, 18-20; figures 1, 5; examples</p>	<p>1-36</p>

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INTERNATIONAL SEARCH REPORT

national Application No
PCT/GB 00/04428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 00 13662 A (HENNINGFIELD JACK E ;CONE EDWARD J (US); JSR LLC (US); PINNEY JOHN) 16 March 2000 (2000-03-16) page 6, last paragraph -page 7, line 1 page 71, line 21 -page 8, line 14 page 9, line 20 - line 26 page 9, line 29 -page 10, line 25; figures page 16, line 8 - line 29 page 24, line 12 -page 25, line 29; claims; examples</p>	<p>1-3,7,9, 10,17, 18,34</p>
T	<p>PARK C R ET AL: "Formulation of a bilayer buccal adhesive tablet for nicotine replacement therapy." JOURNAL OF PHARMACY AND PHARMACOLOGY, vol. 52, no. Supplement, September 2000 (2000-09), page 303 XP000982579 137th British Pharmaceutical Conference;Birmingham, England, UK; September 10-13, 2000 ISSN: 0022-3573 the whole document</p>	<p>1-36</p>

INTERNATIONAL SEARCH REPORT

Information on patent family members

national Application No

PCT/GB 00/04428

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5879710 A	09-03-1999	FR 2718020 A AT 186210 T CA 2186863 A DE 69513157 D EP 0754033 A WO 9526713 A JP 9510986 T	06-10-1995 15-11-1999 12-10-1995 09-12-1999 22-01-1997 12-10-1995 04-11-1997
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(72) Inventors; and

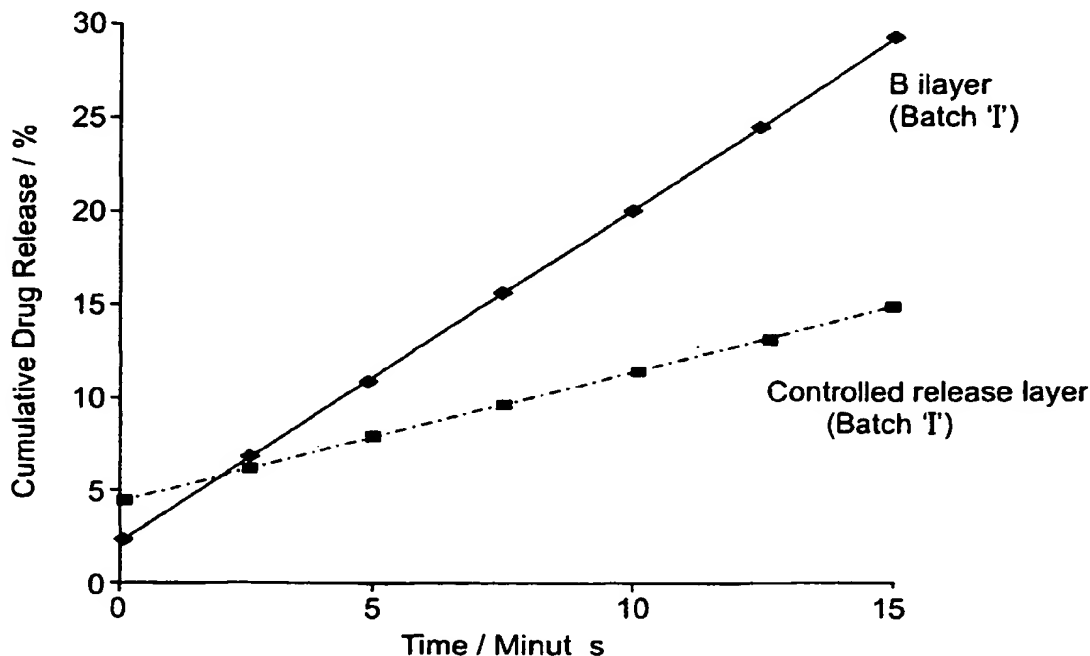
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(74) Agent: **ALLAN, Jamie**; Murgitroyd & Company, 373 Scotland Street, Glasgow G5 8QA (GB).

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[Continued on next page]

(54) Title: BILAYERED BUCCAL TABLETS COMPRISING NICOTINE



(57) Abstract: A method of delivering substance, e.g. a drug, to a subject comprises attaching a tablet or other dosage form to a buccal mucosa, where the dosage form is adapted to release the substance in a multiphasic manner, typically with an initial burst release of substance followed by controlled release over a longer period. The substance is typically nicotine.



(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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BILAYERED BUCCAL TABLETS COMPRISING NICOTINE

1

2

3 This invention relates to the delivery of substances
4 such as bio-active agents and pharmaceuticals to the
5 body. In a preferred embodiment the invention
6 concerns the delivery of nicotine to the buccal area.

7

8 Nicotine replacement therapy (NRT) is a frequent
9 component of strategies to help smokers stop smoking.
10 Present NRT delivery systems include chewing gum and
11 transdermal patches which release the drug over a
12 period of time but do not provide an initial surge of
13 rapidly released drug that mimics the effect of
14 cigarette inhalation; nasal sprays and inhalers are
15 also available which deal with this problem, but
16 these methods do not permit long term release.

17

18 According to the present invention there is provided
19 a method of delivering a substance to the buccal
20 mucosa of a subject, the method comprising providing
21 a tablet comprising a quantity of the substance to be
22 delivered, the tablet having multi-phasic release

1 properties to release controlled amounts of the
2 substance to the subject over time, and releasing the
3 substance from the tablet in the subject's mouth.
4 The invention also provides a tablet for delivery of
5 a substance to the buccal mucosa of a subject, the
6 tablet comprising a quantity of substance to be
7 delivered to the subject, the tablet having multi-
8 phasic release properties adapted to release
9 controlled amounts of the substance to the subject
10 over time.

11
12 The tablet can be of conventional physical design but
13 any vehicle capable of bearing the substance and
14 dissolving in the mouth can be used.

15
16 The tablet may have a multi-layer structure with
17 different amounts of substance associated with each
18 layer. This can be by making different homogeneous
19 layers with different release characteristics or by
20 enclosing different quantities of substance within
21 layers of e.g. coating that can dissolve at different
22 rates, thereby deferring the time until the fluids in
23 the mouth dissolve the substance and/or the tablet
24 matrix.

25
26 The tablet may comprise a bioadhesive such as
27 Carbopol(TM) or chitosan, or a similar bioadhesive
28 polymer, and this can optionally be in a separate
29 adhesive layer, or can be incorporated into another
30 part of the tablet, such as the slow (or controlled)
31 release layer. The inventors have found that these

1 compounds also assist in controlling the release of
2 the substance. The tablet may also contain other
3 agents to control the release of the substance such
4 as hydroxypropylmethyl cellulose, hydroxypropyl
5 cellulose, poly D L lactide- and/or glycolide-
6 related polymers. Such polymers are very useful in
7 the present invention as they swell when hydrating
8 and this can be used to control the release
9 characteristics of the substance which is retarded in
10 the swollen polymer until the polymer starts to
11 dissociate from the tablet. This can be used to
12 change the release characteristics of the tablet
13 without necessarily changing the amount of substance
14 in the tablet, and without layering the tablet. Thus
15 multi-phasic release properties can be achieved with
16 a homogeneous tablet.

17

18 The outer layer of the tablet may be adapted to
19 release a quantity of the substance very quickly to
20 satisfy a craving in the subject for addictive
21 substances.

22

23 Typically the substance is nicotine. Other
24 substances are also suitable such as cannabinoids,
25 antibiotics, analgesics or anaesthetics such as
26 lidocaine for direct application to mouth ulcers etc
27 or for use prior to or following dental treatment,
28 and drugs for other buccal infections. In principle,
29 any drug that is suitable for oral administration can
30 be used in the present invention.

31

1 Excipients that assist in the penetration of the
2 substance through the buccal membrane can be
3 included, such as bile salts.

4
5 The inner layer or layers may be associated with
6 slower release of substance. The layers may contain
7 the substance as an integral component of the layers
8 or the substance may be provided in a separate layer
9 beneath coatings that exhibit the desired release
10 characteristics. For example, the layers may be made
11 up of a material that is adapted to dissolve at a
12 known rate so as to release the substance underneath
13 the layer or trapped within it at a set time after
14 the tablet is placed in the mouth.

15
16 Preferably different layers have different release
17 characteristics. For example the outer layers are
18 preferably capable of releasing substance at a
19 different (preferably faster) rate than the inner
20 layers.

21
22 In a preferred embodiment the tablet formulation
23 consists of two distinct layers, each of which has a
24 specific function. A controlled release layer
25 containing a bioadhesive is attached to the mucosal
26 tissue lining the cheek adjacent to the gum (gingiva)
27 in the buccal area of the patient's mouth. Upon
28 contact with saliva the rapid release layer
29 disintegrates and releases nicotine, which is
30 subsequently absorbed through the oral mucosa into
31 the systemic circulation. This immediate release and

1 absorption of nicotine is designed to reduce or
2 eliminate the cravings for nicotine of the smoker,
3 particularly those following a meal (post-prandial
4 cravings). The time period over which the tablet
5 remains attached to the buccal mucosa typically
6 determines the time period over which nicotine is
7 released. This is potentially up to three or four
8 hours. During this period nicotine is being absorbed
9 into the systemic circulation at a constant rate
10 (referred to as zero order release), independent of
11 the amount of nicotine remaining in the formulation,
12 thus eliminating further cravings for nicotine. The
13 user may, at any time, detach and remove the tablet
14 if they think this appropriate. One possible scenario
15 of usage is removal of the tablet prior to eating a
16 meal followed by attachment of a new tablet following
17 completion of the meal.

18

19 Various doses of nicotine or other substance can be
20 incorporated into the tablet, in both the rapid and
21 controlled release layers, thus allowing flexibility
22 in reducing regimes for patients and tailoring the
23 formulation to individual patterns of craving for
24 nicotine. The incorporation of different doses of
25 drug does not alter the release mechanism; i.e. it
26 remains rapid from the first layer and zero order
27 from the controlled release layer.

28

29 Typical dimensions of the tablet are 6mm diameter and
30 3mm thickness. These dimensions are usefully
31 independent of nicotine or other substance content as

1 any reductions in the same are compensated for by
2 increased amounts of diluent to maintain tablet
3 weight and dimension.

4
5 For mucoadhesion, Carbopol C934 has been extensively
6 studied and been shown to produce excellent adhesion
7 to mucosal membranes. The bioadhesive strength of
8 this poly (acrylic) acid polymer increases with
9 polymer concentration up to 25% w / w and thereafter
10 remains relatively constant and a tablet containing
11 5-50 % C934 can adhere to the gingiva for 550-600
12 minutes. C934 was therefore favoured as the
13 mucoadhesive polymer in the formulation at a
14 preferred concentration of around 20 % w / w where
15 mucoadhesive strength is near maximum and below the
16 50 % concentration, which has the potential to cause
17 some mucosal irritation.

18
19 For controlled drug release from buccal adhesive
20 tablets, HPC is effective in producing controlled
21 drug release.

22
23 The layers of the tablet need not be concentric
24 although in certain embodiments this is preferred.
25 In certain embodiments shown in the examples
26 following the tablet has two (or more) flat layers in
27 a "sandwich" structure.

28
29 Examples of the invention will now be described by
30 way of illustration, and without limiting the scope

1 of the invention, with reference to the accompanying
2 drawings, in which:

3 Fig. 1 is a schematic view of a tablet;
4 Fig. 2 is a graph of representative nicotine
5 release profiles from dosage forms;
6 Fig. 3 is a diagrammatic representation of drug
7 release from a polymer matrix;
8 Fig. 4 is a graph of release of nicotine from a
9 bi-layer tablet;
10 Fig. 5 is a schematic diagram of diffusion
11 apparatus used in the methods described;
12 Fig. 6 is a graph of water uptake profiles for
13 buccal adhesive tablets;
14 Fig. 7 is a graph of NHT dissolution profiles
15 for buccal adhesive formulations;
16 Fig. 8 is a graph of diffusional exponent values
17 for nicotine buccal adhesive tablets;
18 Fig. 9 is a graph of NHT kinetic rate constant
19 values for nicotine buccal adhesive tablets;
20 Fig. 10 is a graph demonstrating the linear
21 relationship between NHT release rates and HPC
22 content of nicotine buccal adhesive tablets
23 using diffusion dissolution apparatus;
24 Figs. 11 and 12 are graphs showing dissolution
25 profiles for bilayer tablets; and
26 Fig. 13 shows drug release profiles of NHT
27 bilayer tablets over the first hour of a 4 hour
28 flow through dissolution test.

29
30 Example 1.
31

1 Controlled release formulations A - F were produced
2 as shown in Table 1.1, containing nicotine in the
3 form of NHT, PVP to act as a binding agent, lactose
4 as a diluent and magnesium stearate as a lubricant.
5 C934 was included to impart adhesive properties and
6 HPC was included in a range of concentrations to
7 investigate its effect on NHT release. PVP (molecular
8 weight 44000) is included as a binding agent, but
9 also has release-controlling properties.
10 Carbopol(TM) 934P is a synthetic high molecular
11 weight cross-linked polymer, which imparts
12 bioadhesive properties on the formulation. In
13 addition this polymer also has release-controlling
14 and binding properties.
15
16 Spray-dried lactose is included as an inert diluent.
17 The physical and chemical properties of this material
18 are ideal for use as such an agent.
19
20 HPC is a semi-synthetic polymeric cellulose
21 derivative which has matrix-forming properties. Once
22 hydrated the drug can diffuse out of the matrix.
23 This material thus has drug release controlling
24 properties.
25
26 Magnesium stearate was optionally added as a glidant
27 and anti-adherent agent which facilitates powder flow
28 (essential for successful tablet production) and
29 prevents adherence of the powder materials to the
30 tooling of the tablet manufacturing apparatus.
31

1 **Table 1.1.** Excipient concentrations used in the
2 preparation of formulations A - F.

<i>Excipient composition of tablet mg / tab</i>						
	A	B	C	D	E	F
NHT	10	10	10	10	10	10
PVP (44,000)	6	6	6	6	6	6
C934	20	20	20	20	20	20
HPC	-	10	20	30	40	50
SDL	63	53	43	33	23	13
MGS	1	1	1	1	1	1

3 NHT = nicotine hydrogen tartrate, PVP = polyvinylpyrrolidone, C934 =
4 carbopol, HPC = hydroxypropylcellulose, SDL = spray dried lactose

5
6 The excipients were weighed accurately and physically
7 mixed by shaking in a bag for 10 minutes. Powder
8 mixes were used to produce 100 mg tablets by direct
9 compression using an eccentric tablet press (model
10 F3, Manesty machines Ltd, Liverpool, UK) using 6 mm
11 punches.

12
13 The dose of nicotine may be varied depending on
14 requirements and a corresponding reduction in
15 mannitol amount maintains tablet dimensions constant.
16 The RRL is optionally formed by mixing the above
17 ingredients and compressing them in a mould of
18 desired shape to form the layer.

19
20 Bilayer nicotine buccal tablets were formulated.
21 Burst release of NHT from a rapid release layer to
22 satisfy a craving for nicotine, followed by prolonged
23 release of nicotine from a controlled release layer
24 to prevent reoccurrence of the nicotine cravings.

1 Rapid release layers (RRL) were formulated using the
2 excipients listed in table 1.2

3

4 **Table 1.2.** Excipient concentrations used in the
5 preparation of RRL layers for bilayer tablet
6 manufacture.

<i>Excipient composition of rapid release layer mg / layer</i>		
	<i>2 mg RRL</i>	<i>5 mg RRL</i>
NHT	2	5
PVP 10,000	4	4
Mannitol	44	41

7

8 The excipients were again physically mixed in a bag
9 for 10 minutes. Bilayer tablets were produced using
10 a 2-stage compression cycle. The controlled release
11 layer (CRL) was first formed by direct compression of
12 powder mixes A - F in table 1.1. The CRL was left in
13 the tablet die and the bottom punch lowered. 50 mg of
14 the RRL was added to the die and the second
15 compression carried out. The bilayer tablets were 6
16 mm x 4.5 mm in dimension and are depicted in figure
17 1. Bilayer tablets containing both 2 mg and 5 mg RRL
18 were prepared with each CRL (A - F).

19

20 The RRL could be distinguished from the CRL layer by
21 the pure white colour of the RRL through the use of
22 mannitol. In a marketed product, the addition of a
23 pharmaceutical pigment would allow the user to
24 distinguish the layers and identify which layer
25 should be attached to the gingiva (gum).

26

27 Example 2.

1 In this example the RRL was as described in example 1
2 above, and the CRL was as follows:

3

4 **Table 2**

5

<i>Amount per tablet / mg (percentage composition)</i>		
Ingredient	CRL 2	
Nicotine	10	(10%)
Magnesium stearate	1	(1%)
PVP*	10	(10%)
Carbopol (TM) 934P	20	(20%)
Spray-dried lactose	19	(19%)
HPC**	40	(40%)

PVP = polyvinyl pyrrolidone, molecular weight 44000.

6 ** HPC = hydroxypropyl cellulose. In each example, the two
7 layers of the overall tablet were separately
8 fabricated; although combined fabrication of whole
9 tablets is generally within the scope of a skilled
10 man. In the present examples the RRL ingredients
11 were mixed and granulated using ethanol as the
12 granulating fluid, followed by compression into
13 tablets; for the CRL the ingredients were dry mixed
14 and tablets formed by direct compression. The two
15 individual tablet layers were then replaced in the
16 die of a tablet press and compressed for a second
17 time, resulting in the formation of one coherent
18 bilayer tablet.

19

20 The tablet manufacturing apparatus employed for the
21 fabrication was a standard single punch eccentric
22 press with no modifications. For the rapid production

1 of larger batches of product a specialised double
2 compression tablet press can be used.

3

4 Results for examples 1 and 2.

5

6 Using standard BP disintegration apparatus it was
7 found that the rapid release layer completely
8 disintegrated within four minutes. This time is
9 considered acceptable to facilitate rapid absorption
10 of nicotine from the oral mucosa thus eliminating the
11 initial craving of the smoker for nicotine.

12

13 The nicotine release from the formulations produced
14 was studied over a four-hour period using standard
15 USP paddle dissolution apparatus and a typical
16 release profile of the results obtained is depicted
17 in Figure 2.

18

19 The drug release profiles demonstrate the biphasic
20 nature of the release from the bilayer formulations:
21 an initial burst release of nicotine followed by
22 retarded zero order drug release. This characteristic
23 is absent from the single layer controlled release
24 tablets, which release drug in a monophasic zero
25 order kinetic manner. The initial burst nicotine
26 release is essentially complete within 30 minutes.
27 This result contradicts the disintegration time of
28 the RRL of 4 minutes. However, differences in the
29 hydrodynamic properties of the two test methodologies
30 account for such contradictory results; nonetheless,
31 it is believed that the faster release initially

1 would sufficiently satisfy initial craving rapidly,
2 and encourage buccal absorption, rather than the
3 swallowing of saliva and consequent unpleasant
4 gastro-intestinal effects.

5
6 The mechanism by which drug release is retarded in
7 the controlled release formulations is thought to be
8 due to the formation of a matrix of drug and
9 polymer(s) during fabrication and subsequent contact
10 with the dissolution medium. The drug is evenly
11 dispersed within this matrix, as shown in Fig 3. The
12 dissolution medium can enter through pores in the
13 matrix, dissolve the drug and the resulting drug
14 solution diffuses out of the matrix.

15
16 This type of mechanism normally results in first
17 order drug release, as diffusion is a first order
18 process, i.e. the rate of diffusion is dependent on
19 the amount of drug remaining in the formulation. The
20 observation of zero order drug release from the
21 formulations produced is thought to be due to a
22 complex combination of drug diffusion, matrix erosion
23 and interaction of oppositely charged nicotine
24 (cationic) with anionic substituent groups on the
25 Carbopol(TM) molecule, i.e. the -COOH groups.

26
27 Example 3

28
29 Table 3.1 below shows the formulation ingredient
30 quantities of the controlled release layer of further
31 embodiments A-I. The rapid release layer contained 2

1 mg NIC, 4 mg PVP 10000 and 44 mg mannitol. The two
 2 layers were produced individually by direct
 3 compression (8mm punch). Bilayer tablets were
 4 produced by manually compressing the two layers
 5 together (Manesty F3, Liverpool, UK).

6

7 **Table 3.1**

8

<i>Sustained release layers produced.</i>									
<i>Mass of ingredient per tablet / mg</i>									
<i>Tablet Formulation Number</i>									
	A	B	C	D	D	F	G	H	I
Ingredient									
NIC	10	10	10	10	10	10	10	10	10
Carbopol	20	20	20	20	20	20	-	-	-
934 (r)	2	4	6	2	4	6	2	4	6
PVP 44000									
HPC	-	-	-	40	40	40	40	40	40
MgS	1	1	1	1	1	1	1	1	1
LactoseTO	100	100	100	100	100	100	100	100	100

PVP = polyvinylpyrrolidone, HPC = hydroxypropylcellulose*

MgS = magnesium stearate

* HPMC can also be used

9

10 In vitro drug release was assessed using a
 11 dissolution cell method in which the tablet was
 12 attached to an artificial dialysis membrane, used to
 13 simulate the buccal mucosa, and the drug was released
 14 through this into a reservoir of distilled water, and
 15 determined by UV spectrophotometry. Other methods
 16 used included USP paddle dissolution methods. Zero
 17 order release profiles were achieved for batches A-I

1 over 4 hours. The following table 3.2 demonstrates
2 batches G-I had the highest release rates due to the
3 absence of Carbopol 934P(r). Release rates were
4 decreased in all batches by increasing concentrations
5 of PVP which resulted in decreased layer swelling.

6 **Table 3.2**

7

<i>Zero order release rates of nicotine (diffusion cell)</i>					
Formulation	A	B	C	D	E
Dissolution	0.26	0.17	0.15	0.25	0.15
Rate / % min-1					
Formulation	F	G	H	I	
Dissolution	0.12	0.37	0.35	0.37	
Rate / % min-1					

8 Equation 1, an exponential expression used to analyse
9 controlled release behaviour of pharmaceutical
10 systems, was employed to investigate the dissolution
11 data (Peppas and Sahlin, 1989 Int. J. Pharmaceutics
12 57:169-172).

13

14 $M_t / M_\infty = kt^n$ - Equation 1

15

16 In this equation, M_t / M_∞ is the fraction of drug
17 released, k is the kinetic constant and n is the
18 diffusion exponent for drug release. This equation
19 can be applied to the first 60 % of drug release to
20 identify the type of drug release from the system. A
21 plot of $\log (M_t / M_\infty)$ versus $\log t$ gives a straight
22 line of gradient n and intercept $\log k$.

23

1 Diffusion cell results ($n = 0.69-0.93$) indicated the
2 overall drug release mechanism was non-Fickian
3 controlled by a combination of NIC diffusion and
4 polymer chain relaxation ($r^2 = 0.88-0.97$).

5

6 Fig. 4 shows release profiles from tablets (US
7 paddle) and demonstrates the efficient release from
8 the rapid release layer of sample I (98% of the
9 nicotine was released after 10 minutes).

10 Example 4

11 Dosage forms formulated as above were tested to
12 ensure that the patient receives a product containing
13 the required amount of drug substance in a form that
14 enables the drug substance to exert its full
15 pharmacological action. The standard tests included
16 uniformity of weight, uniformity of content,
17 disintegration (where appropriate) and dissolution,
18 and the non-standard crushing strength and resistance
19 to abrasion tests.

20

21 Ten tablets from each tablet batch were selected and
22 weighed accurately to 4 decimal places using an
23 analytical balance (model AE 50, Mettler instruments
24 LTD, High Wycombe, U.K.). The tablet weights were
25 averaged and a relative standard deviation value
26 calculated.

27

28 Three tablets from each batch were weighed and the
29 theoretical NHT content was calculated. Each tablet

1 was then powdered and placed in a standard flask and
2 allowed to dissolve in 50 mL of HPLC mobile phase.
3 To facilitate the solution of the water swellable
4 polymers within the tablet matrix, and ensure
5 complete NHT release from the polymers, the flasks
6 were placed in an ultrasonic bath for 60 minutes,
7 left overnight and then placed in the sonic bath for
8 a further 60 minutes. The solutions were filtered
9 under gravity using filter paper, diluted
10 appropriately and the NHT content assayed using an
11 analytical HPLC method.

12

13 The crushing strength test involves application of a
14 compressive load to the tablet to induce breaking.
15 Sophisticated testers apply the force at a constant
16 rate to improve reproducibility over simple hand
17 operated devices. However, even when the load is
18 applied at a constant rate, the variation in strength
19 within a batch may be considerable.

20

21 Five tablets from each batch were placed in a tablet
22 hardness tester (model TBH 28, Erweka, Heusenstamm,
23 Germany). The values were averaged and a relative
24 standard deviation value was calculated.

25

26 It is likely that a tablet, during a normal life,
27 will be exposed to forces in production, packaging or
28 transportation procedures. These forces whilst not
29 severe enough to break the tablet, may abrade small
30 particles from its surface. To assess the resistance
31 to abrasion, a friability tester is used, which

1 subjects tablets to a uniform tumbling action, for a
2 specified time, and the weight loss from the tablets
3 is measured.

4
5 Five tablets from each batch were weighed
6 collectively and the weight noted. The tablets were
7 then placed in a friability tester (model TA, Erweka,
8 Heusenstamm, Germany). After 5 minutes, the five
9 tablets were re-weighed and the percentage weight
10 loss was calculated.

11
12 A swellable matrix is used to control the release of
13 drug, and polymer swelling is an important stage in
14 the formation of a mucoadhesive bond between such
15 formulations and the mucosa. In vitro swelling
16 studies were therefore carried out.

17
18 Three tablets from each batch were placed on a
19 plastic mesh (1 cm²) to allow handling of the tablet
20 without direct touching. The tablet / mesh assembly
21 was weighed accurately to 4 decimal places and the
22 weight noted. The axial and radial dimensions of the
23 tablets were measured using sliding scale callipers.
24 Each tablet assembly was placed in separate glass
25 vials containing 4 ml of deionised water. At
26 specific time intervals over 24 hours, the tablet
27 assembly was removed from the vials and any surface
28 moisture was carefully removed using filter paper.
29 The assembly was re-weighed and the axial and radial
30 dimensions were again noted. The percentage increase

1 in weight, axial and radial dimensions was
2 calculated.

3
4 *In Vitro* NHT dissolution was analysed using two
5 different methods. The first involved flow through
6 dissolution apparatus, where the buccal adhesive
7 tablets were exposed to 20 mL dissolution medium.
8 The second method is a novel method, devised to more
9 accurately represent the *in vivo* conditions to which
10 a buccal adhesive tablet might be exposed. The
11 method used a transdermal tester and following NHT
12 dissolution from the tablet in a small volume (< 0.5
13 mL) the detected NHT diffuses across a membrane in to
14 a 5 mL cell.

15
16 Three tablets from each batch were weighed and the
17 theoretical nicotine contents were calculated and
18 noted. The tablets were placed separately in a 20 mL
19 cell in the flow through dissolution tester. The
20 dissolution medium was distilled water supplied at a
21 flow rate of 100 mLhr⁻¹ by a pump (model 202u, Watson
22 - Marlow, Falmouth, U.K.) and at 37°C from an
23 electric water heater (model W14, Grant Instruments,
24 Cambridge, U.K.). The effluent from the cells was
25 collected over a 4 hour period and assayed at certain
26 time intervals using U.V. detection at 259 nm (model
27 UV 300, Unicam LTD, Cambridge, U.K.).

28
29 A transdermal tester as shown in Fig. 5 (model HDT
30 10, Copley Scientific Ltd., Nottingham, U.K.) was

1 used for testing diffusion of the substance across a
2 cell membrane.

3
4 Tablets from each batch were weighed and the
5 theoretical nicotine contents were calculated and
6 noted. The experimental membrane was secured tightly
7 to the cells, as show above. Single layer visking
8 dialysis membrane or porcine buccal mucosa was used
9 as the test membrane. Buccal mucosa was collected
10 and prepared. Porcine mucosa was used the same day as
11 the animal was sacrificed. The 5 mL cells were then
12 filled with distilled water from the solution
13 reservoir and the clamps secured. The cell stirrers
14 and the cell heater were switched on to heat the
15 solution to 37°C. To start, 100 µL of water was
16 placed on the upper side of the membrane and the
17 tablet was placed gently on the surface. 50 µL of
18 water was added to the tablet and membrane interface
19 at 30 minute intervals using an automatic pipette to
20 maintain adequate wetting of both the tablet and the
21 membrane. At certain time intervals, 5 mL samples
22 were withdrawn from the cells and the nicotine
23 content and hence the percentage nicotine released
24 from the tablet was investigated over a 4 hour period
25 using U.V. analysis. The dissolution runs were
26 repeated in triplicate for each batch. The area
27 available for drug permeation in to solution was
28 0.785 cm².

29
30 The results of the uniformity of weight experiment
31 are tabulated in table 4.1.

1 **Table 4.1.** Uniformity of weight for batches A - F
2 (n=10) .

Tablet	A	B	C	D	E	F
Mean Weight / mg	100.69	100.10	100.31	100.32	99.90	100.29
(RSD / %)	(0.732)	(0.309)	(0.268)	(0.387)	(0.293)	(0.394)

3 The expected weight of the tablets was 100 mg. All
4 tablet weights were 100 mg \pm 2 mg. The average
5 weight from 10 tablets in each batch was 100 mg \pm 1
6 mg. Additionally the variation in tablet weights
7 within each batch was very low as indicated by the
8 low percentage relative standard deviation values in
9 table 4.1. It can therefore be concluded that the
10 dry mixing and direct compression of the tablets
11 produces a uniform batch with regard to tablet
12 weight.

13
14 The NHT recovered during the assay is quoted as a
15 percentage of the theoretical NHT in the tablet (10 %
16 of tablet weight). The mean percentage NHT recovered
17 for each tablet batch is tabulated below in table
18 4.2.

19
20 **Table 4.2.** Uniformity of active ingredient for
21 batches A - F (n=3) .

Tablet	A	B	C	D	E	F
Mean NHT	98.74	98.60	100.15	97.66	96.70	95.78
recovered / %	(3.95)	(1.88)	(3.23)	(2.46)	(1.23)	(0.78)
(RSD / %)						

22
23 The assay results showed that not one tablet
24 contained greater or less than 5 % of the theoretical
25 nicotine content of the tablet. Combined with the

low deviation of tablet weights means that the tablets contained $10 \text{ mg} \pm 0.5 \text{ mg}$ NHT. These results fall well within the limits of 90 - 110% set out by the British Pharmacopoeia. The low standard deviations achieved again confirm that the method of tablet manufacture is suitable for producing uniform tablet batches.

The mean tablet crushing strengths are shown below in table 4.3.

Table 4.3. Tablet crushing strength for batches A - F (n=5).

Formulation	A	B	C	D	E	F
Mean crushing strength / Newtons (RSD / %)	156.0 (5.82)	140.8 (10.52)	142.6 (8.31)	154.4 (4.16)	174.6 (3.05)	183.6 (0.98)

Few conclusions may be drawn from the data in table 4.3. Formulations A - D do not show marked differences in crushing strength and combined with the relatively large standard deviations firm conclusions may not be drawn. Formulations E and F with 40 % and 50 % HPC show slightly higher crushing strengths than the other formulations, perhaps due to the ability of HPC to act as a binding agent. There are no recommendations for buccal release tablets and as the tablets are designed to swell as opposed to disintegrate and dissolve as with an oral tablet, the higher values noted are perhaps appropriate.

1 The percentage weight loss of five tablets from each
2 batch after 5 minutes friability testing is tabulated
3 in table 4.4.

4
5 **Table 4.4. Tablet friability results; Weight loss**
6 **from batches A - F.**

Tablet	A	B	C	D	E	F
Weight loss / %	0.12	0.06	0.06	0.02	0.08	0

7
8 As discussed earlier, the friability tests are
9 designed to simulate conditions that may be
10 experienced by a tablet during production, packaging
11 and transportation. The weight loss from the tablets
12 has been demonstrated to be extremely low perhaps as
13 a function of the tablet hardness. These results
14 indicate that such a formulation would be resistant
15 to abrasion and therefore resistant to loss of tablet
16 weight including the loss of active ingredient
17 through normal processes until the product is used.

18
19 The water uptake profiles of formulations A- F are
20 shown in figure 6.

21
22 As can be clearly seen from figure 6, the swelling
23 profile formulation A is considerably greater than
24 observed for formulations B - F. Over the first 6
25 hours, formulation A has a more rapid weight increase
26 due to a greater uptake of water. The formulation
27 then continues to take up water over the 24 hour test
28 period resulting in a 175.5 % (± 2.55 % RSD) weight
29 increase compared with the dry tablet weight. This

1 larger and more rapid weight increase is due to the
2 absence of HPC from the formulation, which allows the
3 hydrophilic polymer carbopol to uptake the water in
4 to the buccal tablet. Figure 6 also indicates that
5 there is little or no difference between the swelling
6 profiles of formulations B - F, which contain between
7 10 and 50 % HPC. These formulations do not swell
8 to a great extent after the first 6 hours.

9 Formulation B gains an average of 13.5 % in weight
10 between 6 and 24 hours, formulations C - F gain
11 between 1.39 and 4.27 %, which suggests that the
12 formulations are approaching maximal swelling at
13 approximately 6 hours. The addition of HPC to the
14 formulation appears to counteract the strong swelling
15 properties of carbopol, this may be explained by the
16 hydrated matrix properties of HPC which controls the
17 penetration of water into the tablet. Concentrations
18 of 20 - 50 % HPC show no significant difference in
19 weight gain (swelling rate) between 6 - 24 hours.

20

21 The tablet dimensions measured over the 24 hour
22 period showed similar trends compared to the weight
23 increase. Despite large experimental standard
24 deviations (2.5 - 33 % RSD), due to the difficulty of
25 measuring a soft hydrated tablet, an increase in the
26 HPC concentration of the formulation resulted in a
27 smaller size increase of the tablet. The dimensions
28 of formulation A increased to a larger extent than
29 formulations B - F, which swelled to a comparable
30 extent. This may again be explained by the matrix
31 forming properties of HPC, which controls the uptake

1 of water by the formulation. The tablet size
 2 increase for formulations B - F between 6 and 24
 3 hours is again very small, again suggesting that at 6
 4 hours the tablets are approaching maximal swelling.
 5 The actual data is recorded in tables 4.5. and 4.6.

6

7 **Table 4.5. Axial swelling of buccal bioadhesive**
 8 **tablets**

<i>Time / Hours</i>	<i>Axial size increase / %</i>					
	<i>A</i>	<i>B</i>	<i>C</i>	<i>D</i>	<i>E</i>	<i>F</i>
0.5	11.92	14.70	9.36	12.16	14.76	5.28
1	17.02	20.57	13.10	23.83	26.19	9.72
2	28.84	28.43	29.00	32.71	34.76	10.28
3	33.99	30.39	29.95	35.03	34.29	14.45
4	38.54	30.88	36.45	36.91	35.72	17.39
6	47.13	32.84	38.35	37.38	40.48	20.82
24	60.23	43.14	35.08	37.38	37.14	27.20

9

10 **Table 4.6. Radial swelling of buccal bioadhesive**
 11 **tablets**

<i>Time / Hours</i>	<i>Radial size increase / %</i>					
	<i>A</i>	<i>B</i>	<i>C</i>	<i>D</i>	<i>E</i>	<i>F</i>
0.5	14.17	11.11	14.44	11.39	13.89	6.32
1	15.56	13.33	15.00	15.00	15.28	13.56
2	23.33	19.45	18.89	22.67	17.50	19.37
3	28.89	20.56	22.22	21.39	17.50	20.34
4	32.50	25.56	27.78	26.39	17.22	28.05
6	37.78	26.11	32.22	27.78	22.78	27.60
24	60.00	35.28	32.78	30.83	28.61	27.62

12 One theoretical model of mucoadhesion suggests that 3
 13 stages are involved, namely; intimate contact,
 14 interpenetration of mucus / polymer macromolecules
 15 and formation of secondary non-covalent bonds.
 16 Intimate contact between the mucoadhesive and the

1 mucus requires the swelling and spreading of the
2 bioadhesive material to result in a close or intimate
3 contact. The axial tablet dimension, which would be
4 in contact with the mucosal membrane, swells on
5 average by 11.3 % in 30 minutes and should be
6 sufficient to produce the intimate contact required
7 for mucoadhesion.

8
9 The swelling study may also be of importance when
10 assessing the dissolution behaviour of these
11 formulations. HPC, a semi-synthetic polymeric
12 derivative of cellulose, will swell in an aqueous
13 medium to form a gel-like matrix that controls
14 release by acting as a barrier to drug dissolution
15 and diffusion. The HPC gel acts as a physical barrier
16 through which the dissolution medium must penetrate
17 to dissolve the drug, the drug solution must then
18 again penetrate the gel to be available for
19 absorption. Carbopol on the other hand is
20 hydrophilic and will swell faster and to a greater
21 extent, promoting the penetration of the dissolution
22 medium into the tablet matrix. The alteration of
23 polymer content of the matrix will alter the drug
24 release rate. Formulation A containing no HPC should
25 allow the dissolution medium to penetrate the tablet,
26 dissolve the drug and diffuse out of the tablet,
27 resulting in rapid drug release. Formulations B - F
28 containing increasing HPC content should retard drug
29 release by forming the gel barrier resulting in
30 controlled drug release over a number of hours. Due
31 to the small differences in swelling of formulations

1 B - F, it is not possible to predict any differences
2 with regard to drug dissolution.

3

4 Nicotine release profiles for formulations A - F are
5 shown in figure 7.

6 From figure 7 it can be seen that only approximately
7 50 - 60 % drug release was achieved from the
8 formulations. HPC was expected to control the
9 release in such a manner over the 4 hour period, it
10 is therefore surprising that formulation A containing
11 no HPC released only 60 % of NHT in this time.

12

13 The dissolution data was investigated using equation
14 1 as defined above (Peppas and Sahlin, 1989). The
15 data from these plots are presented in table 4.8.

16

17 The calculated n value allows the release mechanism
18 from a cylindrical system such as a tablet to be
19 characterised according to table 4.7. (Peppas and
20 Sahlin 1989).

21

22 **Table 4.7.** Diffusion exponent and solute release
23 mechanism

<i>Diffusion exponent (n) from a cylinder</i>	<i>Release mechanism</i>
0.45	Fickian Diffusion
0.45 < n < 0.89	Anomalous transport
0.89	Case II transport

24

25 Fickian diffusion describes t^{-2} kinetics and case II
26 transport describes constant zero order drug release.
27 Polymer swelling and drug diffusion through a matrix

do not normally follow Fickian release behaviour, due to the existence of a molecular relaxation process (Vigoreaux and Ghaly 1994 Drug Development and Industrial Pharmacy 20(16) 2519-2526). This type of drug release results in intermediate values for n and is classed as anomalous (non Fickian) transport.

Table 4.8. Diffusional exponents (n) and kinetic constants (k) for NHT dissolution from buccal adhesive nicotine tablets ($n=3$).

Formulation	Diffusional exponent (n) (RSD / %)	Kinetic constant / hr^{-1} (k) (RSD / %)	r^2 (RSD / %)	Release mechanism
A	0.6857 (12.05)	0.2520 (14.07)	0.974 (0.27)	Anomalous transport
B	0.7200 (6.75)	0.2174 (7.20)	0.987 (0.59)	Anomalous transport
C	0.8413 (2.83)	0.1940 (4.19)	0.982 (0.84)	Anomalous transport
D	0.8341 (5.31)	0.1855 (0.22)	0.994 (0.73)	Anomalous transport
E	0.7778 (9.26)	0.1905 (3.85)	0.976 (1.40)	Anomalous transport
F	0.7768 (9.78)	0.1915 (8.71)	0.983 (0.357)	Anomalous transport

The n value for formulation A is almost exactly mid range for anomalous non-Fickian release mechanism. However, the n value increases in the other formulations that contain HPC. Formulations C and D containing 20 and 30 % HPC respectively show n values approaching case II transport i.e. zero order NHT release. For formulations E and F containing 40 and

1 50 % HPC, the n values appear to tail off. This
2 suggests the most appropriate matrix for NHT release
3 contains around 20 - 30 % HPC providing release
4 approaching zero order. The variation of the
5 diffusional exponent (n) with HPC is summarised in
6 figure 8.

7
8 The kinetic rate constants (k) in table 4.8
9 incorporate the structural and geometrical
10 characteristics of the release device and may be used
11 to compare formulations. Formulation A, containing
12 no HPC exhibits the greatest rate constant (k). The
13 addition of HPC, as a matrix former results in a
14 decrease in the rate constant as the hydrated HPC
15 provides a barrier to drug dissolution. The rate
16 decreases to a minimum at 30 % and remains relatively
17 constant with increasing HPC concentration. The
18 variation in kinetic rate constant with HPC content
19 is shown graphically in figure 9.

20
21 NHT dissolution using the diffusion dissolution
22 method followed zero order release kinetics using the
23 dialysis visking tubing as the model membrane. The
24 dissolution statistics are presented in table 4.9.

1 **Tabl 4.9.** NHT release rates from nicotine buccal
2 adhesive tablets (n=3)

Formulation	Release rate / %hr ⁻¹ (RSD / %)		r ² (RSD / %)	
A	4.4969	(2.41)	0.989	(0.58)
B	3.9375	(3.42)	0.938	(4.23)
C	3.4169	(2.66)	0.983	(0.53)
D	2.7309	(9.54)	0.983	(0.52)
E	2.8778	(7.91)	0.984	(1.45)
F	2.6863	(16.02)	0.994	(0.34)

3
4 Zero order case II transport was confirmed by
5 analysis of the dissolution data using equation 1 as
6 described above. Diffusion exponent (n) values were
7 between 0.89 and 1.45 in all formulations except
8 formulation B (n = 0.75). The lower correlation
9 value and larger RSD value for formulation B in table
10 4.9. may explain this.

11
12 The release rates quoted in table 4.9. again appear
13 to decrease with increasing HPC concentration. This
14 decrease in release rate appears to be linear to a
15 concentration of 30 % as can be seen in figure 10.

16
17 HPC contents of 30 % and above (formulations D, E and
18 F) produce NHT release rates that are not
19 significantly different (p > 0.05). This agrees with
20 the trend shown by the NHT release for the flow
21 through dissolution method and suggests that HPC
22 concentrations of above 30 % are not necessary to
23 produce a sustained release matrix for NHT.

24 It is worth noting that the release rates across the
25 dialysis visking tubing for formulation A are not
26 significantly different from the permeation rates of

1 nicotine from solution through the same membrane seen
2 in section 3.3.4.1. This suggests that limiting
3 factor to drug dissolution using this method is in
4 fact permeation across the membrane resulting in zero
5 order kinetics. When HPC is present in the
6 formulation, however, these rates decrease further.
7 Over the 4 hours, a maximum of 17 % NHT was released,
8 this decreased to 11.5 % for formulation F. When
9 compared with the results from the flow through
10 dissolution (50 - 60 %) this value is low, but may be
11 due to the nature of the membrane.

12

13 The diffusion dissolution apparatus was set up using
14 porcine buccal membrane. Due to the limited supply
15 of porcine mucosa, this experiment was carried out
16 once with formulation A. Using HPLC detection, only
17 1.4 % of the NHT content of the tablet was recovered
18 in the receptor solution after 4 hours. This figure
19 is very low compared with the artificial membrane and
20 may be due to the thickness of the membrane and
21 problems of using animal tissue. The experiment was
22 repeated using formulation A and fresh porcine
23 mucosa, however instead of sampling from the receptor
24 solution, after 4 hours that tablet was assayed to
25 determine the NHT remaining in the formulation.
26 Following this method, the HPLC tablet assay detected
27 6.95 mg of NHT remaining, which was calculated to be
28 69 % of the NHT content of the tablet. It could
29 therefore be concluded that 31 % of the available NHT
30 (3.11 mg) had been released from the tablet. All the
31 NHT release was not able to cross the porcine

1 membrane and enter the receptor solution, most likely
2 due to the 2 mm thickness of the membrane (the upper
3 200 μm is known to be the barrier to buccal
4 permeation) and the small orifice (0.785 cm^2)
5 available for the NHT to enter the receptor solution.
6 From this data it is suggested that the NHT has been
7 released from the formulation and partitioned into
8 the buccal tissue; however due to the reasons
9 mentioned above, the NHT remained in the tissue and
10 was not passed into the receptor solution.

11
12 All bilayer tablets weighed $150 \text{ mg} \pm 3 \text{ mg}$. The
13 average weights of 3 tablets from all batches ranged
14 from 149.0 mg to 150.5 mg with a corresponding
15 percentage relative standard deviation value of 0.17
16 % to 1.19 %. These results suggest that the method
17 of preparation is suitable in producing bilayer
18 tablets of uniform weight.

19
20 Two formulations were selected in the determination
21 of active ingredient content, formulation CRL B + RRL
22 2 mg and formulation CRL D + RRL 5 mg. The NHT
23 recovered during the assay is quoted as a percentage
24 of the theoretical NHT in the tablet.

25
26 Table 4.10. Uniformity of active content for two
27 bilayer tablet formulations (n=3).

CRL	RRL	Mean NHT recovered / %	RSD / %
A	2	98.52	1.73
D	5	98.88	1.08

28

1 All of the tablets assayed contained $100 \% \pm 2.5 \%$ of
2 the theoretical NHT content. This, combined with the
3 low deviations quoted in table 4.10 again suggests
4 that the method of manufacture of the bilayer tablets
5 is suitable for producing a tablet of uniform active
6 content.

7 One bilayer tablet formulation was selected to carry
8 out the crushing strength determination using the
9 method outlined for formulations A - F. The mean
10 crushing strength ($n=5$) for formulation CRL B + RRL 2
11 mg was 167.4 N (5.08 % RSD). This value is
12 significantly higher ($p < 0.05$) than the formulation
13 B controlled release monolayer alone. This is
14 probably due to the double compression cycle of the
15 bilayer tablet resulting in a harder tablet.

16
17 Formulation CRL B + RRL 2 mg was again used for the
18 friability determination using the method outline for
19 formulations A - F. During the 5 minute friability
20 test, 5 tablets lost 0.15 % of their combined weight.
21 This is higher than the 0.06 % for formulation B
22 controlled release monolayers alone, however this
23 value is still low. The two layers remained joined
24 and intact after the 5 minute test. This suggests
25 that the bilayer tablets would be resistant to
26 abrasion and therefore resistant to loss of tablet
27 weight, including the loss of active ingredient,
28 through normal processes until the product is used.

29
30 NHT release from the bilayer tablets was analysed
31 using the flow through dissolution method outlined

1 above. Release profiles for bilayer tablets
2 containing controlled release layers A and E are
3 shown in figures 11 and 12. These profiles are
4 representative of the trends seen in the release
5 behaviour of all bilayer tablets.

6
7 Figures 11 and 12 show that the bilayer tablets
8 produce a biphasic drug release profile, with a more
9 rapid release of nicotine over the first hour of
10 dissolution testing. Additionally, the rate of drug
11 release from the bilayer tablet with the 5 mg RRL was
12 greater than that from the bilayer tablet containing
13 the 2 mg RRL. This trend was seen in all bilayer
14 tablet batches produced. The bilayer tablets
15 containing the 2 mg RRL released all the NHT content
16 in, on average 26.25 minutes, ranging from 25 to 30
17 minutes (n=18). The 5 mg RRL released all the NHT in,
18 on average 43.3 minutes, ranging from 40 - 47.5
19 minutes (n=18).

20
21 After 1 hour, the drug release profiles level out and
22 appear parallel to tablets containing no RRL. This
23 trend was confirmed by analysis of the dissolution
24 data from 1 to 3 hour time period. There was no
25 significant difference ($p > 0.05$, $n=3$) in the
26 gradients of the lines (release rates) over this time
27 scale for the CRL alone, the CRL and 2 mg RRL and the
28 RRL and 5mg RRL bilayer tablets. This confirmed that
29 after one hour, release rates were governed by the
30 CRL alone with no contribution by the RRL.

31

1 To determine the NHT release profile of the RRL over
2 the first hour of dissolution testing, bilayer
3 tablets containing CRL A and CRL B with the 2 mg RRL
4 were subjected to flow through dissolution over one
5 hour with more frequent sampling times. The NHT
6 release profiles are shown in figure 4.10.

7
8 Figure 4.10. indicates that the NHT release from
9 bilayer tablets over the first hour followed zero
10 order release kinetics. The time taken for the
11 bilayer tablet to release the 2 mg NHT was 27.78
12 minutes (8.44 % RSD). This compares favourably to
13 the 26.35 minutes identified above. Due to the
14 agreement in results, the one hour dissolution
15 experiment was not repeated with the 5 mg RRL.

16
17 Dissolution data was again analysed using equation 1.
18 The results are presented in table 4.11.

19
20 **Table 4.11.** Diffusional exponents (n) and kinetic
21 constants (k) for NHT dissolution from buccal
22 adhesive nicotine tablets (n=3).

1

CRL	RRL	Diffusional Exponent (n) (RSD / %)	Kinetic Constant / hr ⁻¹ (k) (RSD / %)	r ² (RSD / %)	Release Mechanism
A	-	0.6857 (12.05)	0.2520 (14.07)	0.974 (0.27)	Anomalous transport
A	2	0.6383 (19.10)	0.3341 (11.55)	0.965 (0.79)	Anomalous transport
A	5	0.5926 (9.86)	0.3717 (4.51)	0.946 (0.65)	Anomalous transport
B	-	0.7200 (6.75)	0.2174 (7.20)	0.987 (0.59)	Anomalous transport
B	2	0.5882 (20.71)	0.3426 (13.74)	0.962 (1.14)	Anomalous transport
B	5	0.4961 (3.57)	0.3896 (6.02)	0.929 (1.59)	Anomalous transport
C	-	0.8413 (2.83)	0.1940 (4.19)	0.982 (0.84)	Anomalous transport
C	2	0.6020 (13.94)	0.3444 (8.33)	0.970 (2.06)	Anomalous transport
C	5	0.4853 (6.80)	0.4154 (6.26)	0.932 (2.02)	Anomalous transport
D	-	0.8341 (5.31)	0.1855 (0.22)	0.994 (0.73)	Anomalous transport
D	2	0.7075 (3.23)	0.2894 (5.52)	0.956 (1.05)	Anomalous transport
D	5	0.4695 (26.60)	0.4128 (12.84)	0.962 (2.08)	Anomalous transport
E	-	0.7778 (9.26)	0.1904 (3.85)	0.976 (1.40)	Anomalous transport
E	2	0.5639 (12.77)	0.3402 (7.35)	0.988 (0.91)	Anomalous transport
E	5	0.5023 (8.00)	0.4066 (2.46)	0.945 (1.06)	Anomalous transport
F	-	0.7768 (9.78)	0.1915 (8.71)	0.983 (0.983)	Anomalous transport
F	2	0.5892 (20.00)	0.3024 (8.57)	0.938 (3.27)	Anomalous transport
F	5	0.4823 (10.21)	0.3588 (8.36)	0.921 (4.35)	Anomalous transport

1 The calculated n values are all within the range
2 indicating anomalous non-Fickian release mechanism.
3 However table 4.11. indicates that the n values for
4 the bilayer tablets containing 5 mg RRL are lower
5 than for the bilayer tablet containing the 2 mg RRL
6 and both are lower than the CRL monolayers alone.
7 The n values for the monolayers, as discussed
8 earlier, approached zero order release. The addition
9 of the 5 mg RRL results in this value decreasing and
10 the mechanism of release, although still anomalous
11 transport, now approaches Fickian type release where
12 drug release occurs by diffusion of the drug due to a
13 chemical potential gradient. The departure from zero
14 order release may be explained by the distinct
15 biphasic release profiles identified above, where
16 rapid release from the RRL occurs over the first
17 hour, followed by NHT release approaching zero order
18 kinetics over the remaining 3 hours.
19
20 Modifications and improvements can be incorporated
21 without departing from the scope of the invention.
22 For example in many embodiments the tablet can
23 include a sugar such as mannitol, sucrose or glucose
24 that can contain the substance to be released within
25 the tablet and can also improve the taste of the
26 tablet in the mouth. Any sugar can be suitable for
27 this purpose.

1 Claims

2

- 3 1. A method of delivering a substance to the
4 buccal mucosa of a subject, the method
5 comprising providing a tablet comprising a
6 quantity of the substance to be delivered, the
7 tablet having multi-phasic release properties
8 to release controlled amounts of the substance
9 to the subject over time, and releasing the
10 substance from the tablet in the subject's
11 mouth.
- 12
- 13 2. A method as claimed in claim 1, wherein the
14 tablet has a multi-portion structure and
15 different amounts of substance are released
16 from each portion.
- 17
- 18 3. A method as claimed in claim 1 or claim 2,
19 wherein the tablet has a multi-portion
20 structure and the different portions release
21 substance at different rates.
- 22
- 23 4. A method as claimed in any preceding claim,
24 wherein the tablet is attached to the buccal
25 mucosa by a bioadhesive.
- 26
- 27 5. A method as claimed in claim 4, wherein the
28 bioadhesive comprises one or more of carbopol,
29 chitosan, hydroxypropyl cellulose, sodium
30 carboxymethyl cellulose, hydroxypropylmethyl
31 cellulose.

- 1 6. A method as claimed in claim 4 or claim 5,
2 wherein the bioadhesive is disposed in a
3 localised portion of the tablet.
4
- 5 7. A method as claimed in any preceding claim,
6 wherein the tablet contains agents to control
7 the release of the substance.
8
- 8 8. A method as claimed in claim 7, wherein the
9 release-controlling agents comprise one or more
10 of hydroxypropylmethyl cellulose, hydroxypropyl
11 cellulose, poly D L lactide- and glycolide-
12 related polymers.
13
- 14 9. A method as claimed in any preceding claim,
15 wherein a portion of the tablet releases a
16 quantity of the substance quickly to satisfy a
17 craving in the subject for addictive
18 substances.
19
- 20 10. A method as claimed in any preceding claim,
21 wherein the substance comprises one or more of
22 nicotine, cannabinoids, antibiotics, analgesics
23 and anaesthetics.
24
- 25 11. A method as claimed in any preceding claim,
26 wherein the substance is provided in a
27 localised portion having a coating that
28 exhibits the desired release characteristics.
29
- 30 12. A method as claimed in any preceding claim,
31 wherein the tablet is a multi-layer tablet and

1 the layers have different release
2 characteristics.

3

4 13. A method as claimed in claim 12, wherein an
5 outer layer releases substance at a faster
6 rate than an inner layer.

7

8 14. A method as claimed in any preceding claim,
9 wherein the tablet formulation comprises a
10 controlled release layer containing a
11 bioadhesive for attachment to the buccal mucosa
12 and release of substance at a constant rate,
13 and a rapid release layer for rapid release of
14 substance into the systemic circulation through
15 the oral mucosa.

16

17 15. A method as claimed in any preceding claim,
18 wherein the tablet comprises concentric layers.

19

20 16. A method as claimed in any one of claims 1-14,
21 wherein the tablet has two (or more) flat
22 layers in a sandwich structure.

23

24 17. A tablet for delivery of a substance to the
25 buccal mucosa of a subject, the tablet
26 comprising a quantity of substance to be
27 delivered to the subject, the tablet having
28 multi-phasic release properties adapted to
29 release controlled amounts of the substance to
30 the subject over time.

31

- 1 18. A tablet according to claim 17, having a multi-
2 portion structure with different rates of
3 release of substance associated with each
4 portion.
5
- 6 19. A tablet according to claim 18, having
7 different homogeneous portions with different
8 release characteristics.
9
- 10 20. A tablet according to claim 18 or claim 19,
11 having different quantities of substance
12 associated with respective portions.
13
- 14 21. A tablet according to any one of claims 18-20,
15 wherein an inner portion is adapted for slower
16 release of substance than an outer portion.
17
- 18 22. A tablet according to any one of claims 18-21,
19 wherein the outer portion of the tablet is
20 adapted to release a quantity of the substance
21 quickly.
22
- 23 23. A tablet according to any one of claims 18-22,
24 wherein the respective portions contain a
25 homogeneous dispersion of the substance
26 throughout each portion.
27
- 28 24. A tablet according to any one of claims 18-23,
29 wherein the substance is provided in a discrete
30 portion having a coating that exhibits the
31 desired release characteristics.

- 1 25. A tablet according to any one of claims 17-24
2 wherein the tablet has a multi-layer structure.
3
- 4 26. A tablet according to claim 25, wherein the
5 layers of the tablet are concentric.
6
- 7 27. A tablet according to claim 25, wherein the
8 tablet has two or more flat layers in a
9 sandwich structure.
10
- 11 28. A tablet according to any one of claims 17-27,
12 comprising a bioadhesive.
13
- 14 29. A tablet according to any one of claims 17-28,
15 having a controlled release layer containing a
16 bioadhesive for attachment to the buccal mucosa
17 and sustained release of the substance at a
18 relatively constant rate, and a rapid release
19 layer for rapid release of the substance upon
20 contact with saliva in the mouth.
21
- 22 30. A tablet according to claim 28 or 29, wherein
23 the bioadhesive is in a localised portion of
24 the tablet.
25
- 26 31. A tablet according to any one of claims 28-30,
27 wherein the bioadhesive comprises one or more
28 of carbopol, chitosan, hydroxypropyl cellulose,
29 sodium carboxymethyl cellulose,
30 hydroxypropylmethyl cellulose.
31

- 1 32. A tablet according to any one of claims 17-31,
2 containing agents to control the release of the
3 substance.
4
- 5 33. A tablet according to claim 32, wherein the
6 agent comprises one or more of
7 hydroxypropylmethyl cellulose, hydroxypropyl
8 cellulose, poly D L lactide- and glycolide-
9 related polymers.
10
- 11 34. A tablet according to any one of claims 17-33,
12 wherein the substance is nicotine.
13
- 14 35. A tablet according to any one of claims 17-33,
15 wherein the substance comprises one or more of
16 cannabinoids, antibiotics, analgesics and
17 anaesthetics, and drugs for buccal infections.
18
- 19 36. A homogeneous tablet according to claim 18.

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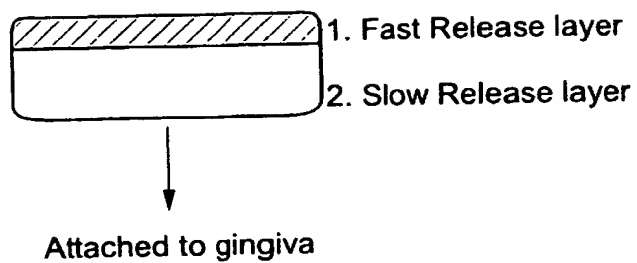
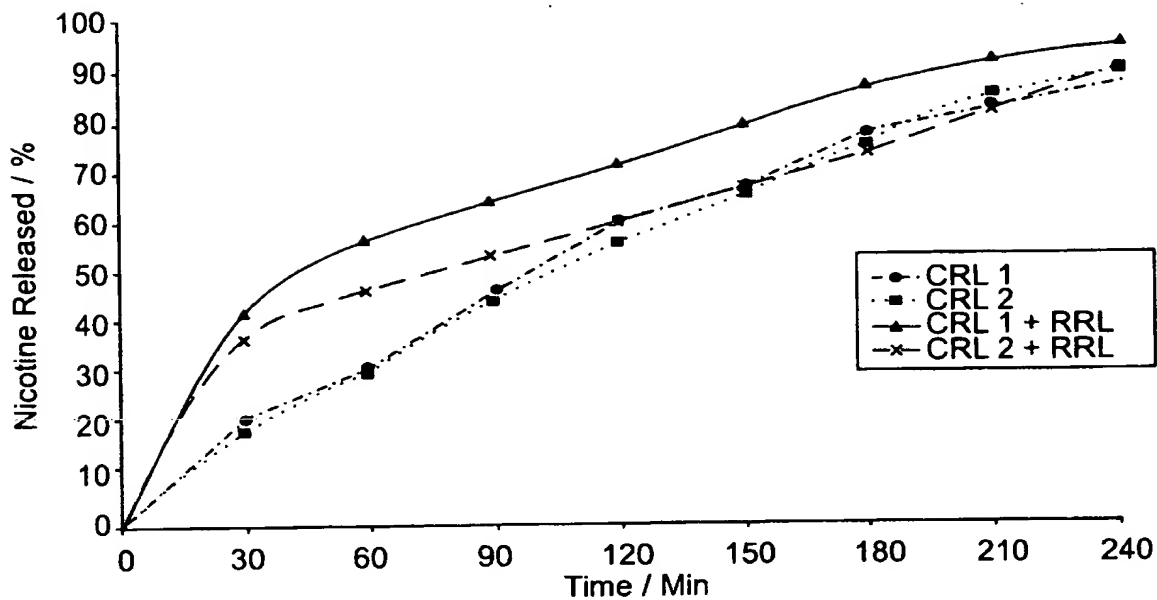
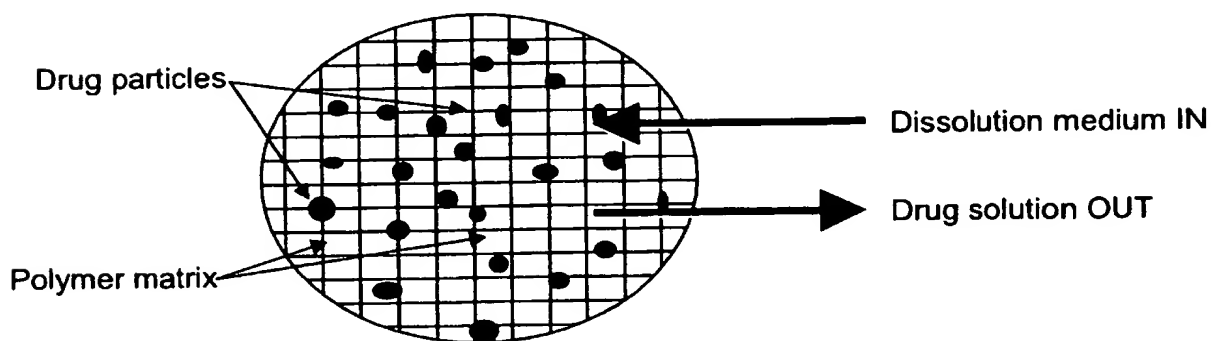


Fig. 1

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*Fig. 2**Fig. 3*

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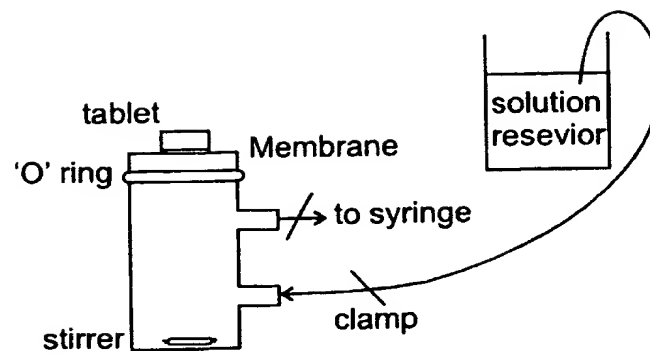


Fig. 5

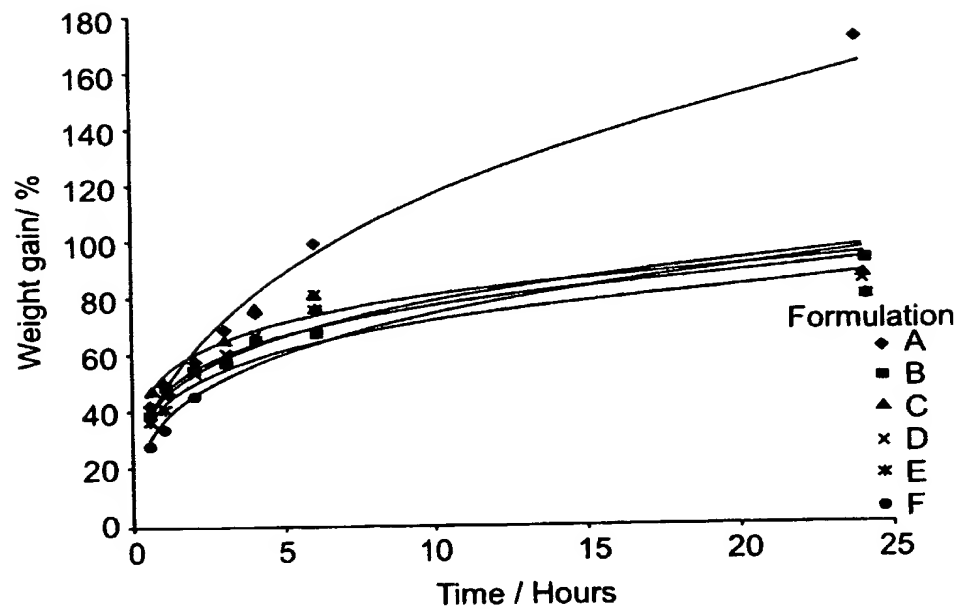
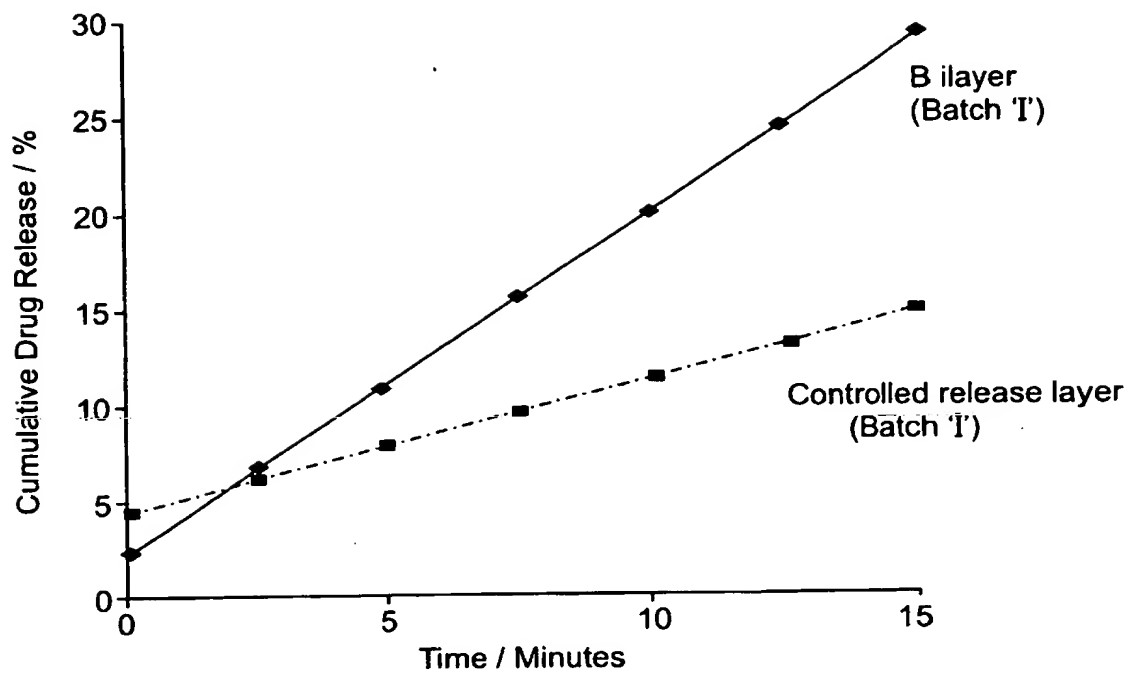
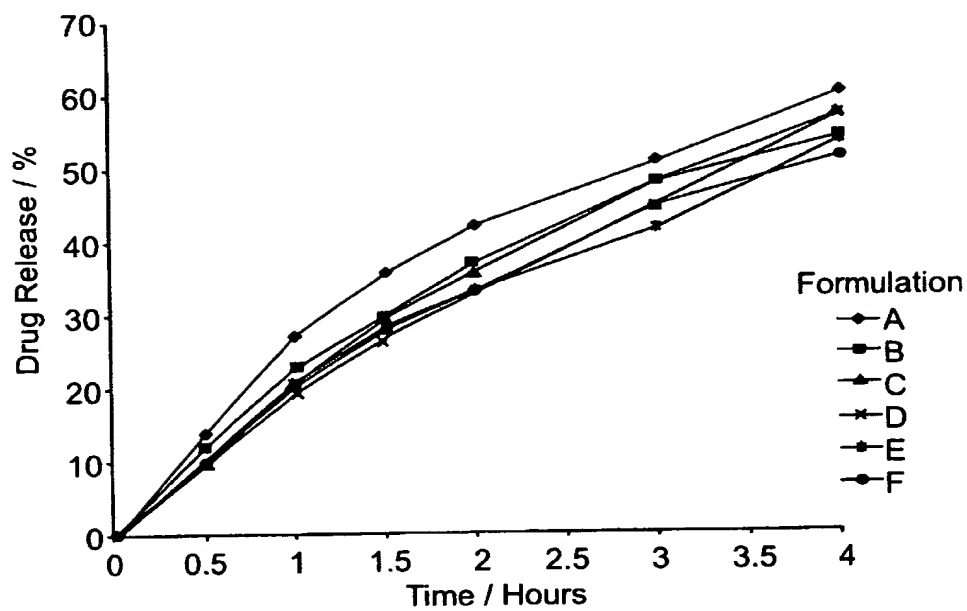


Fig. 6

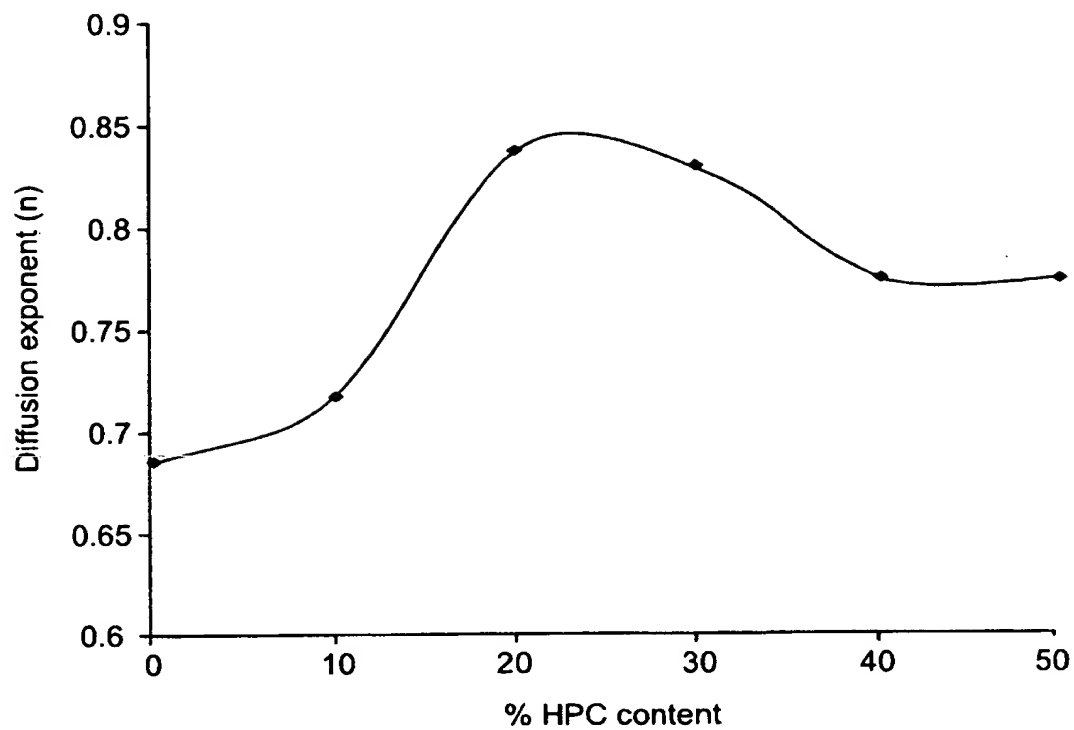
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*Fig. 4*

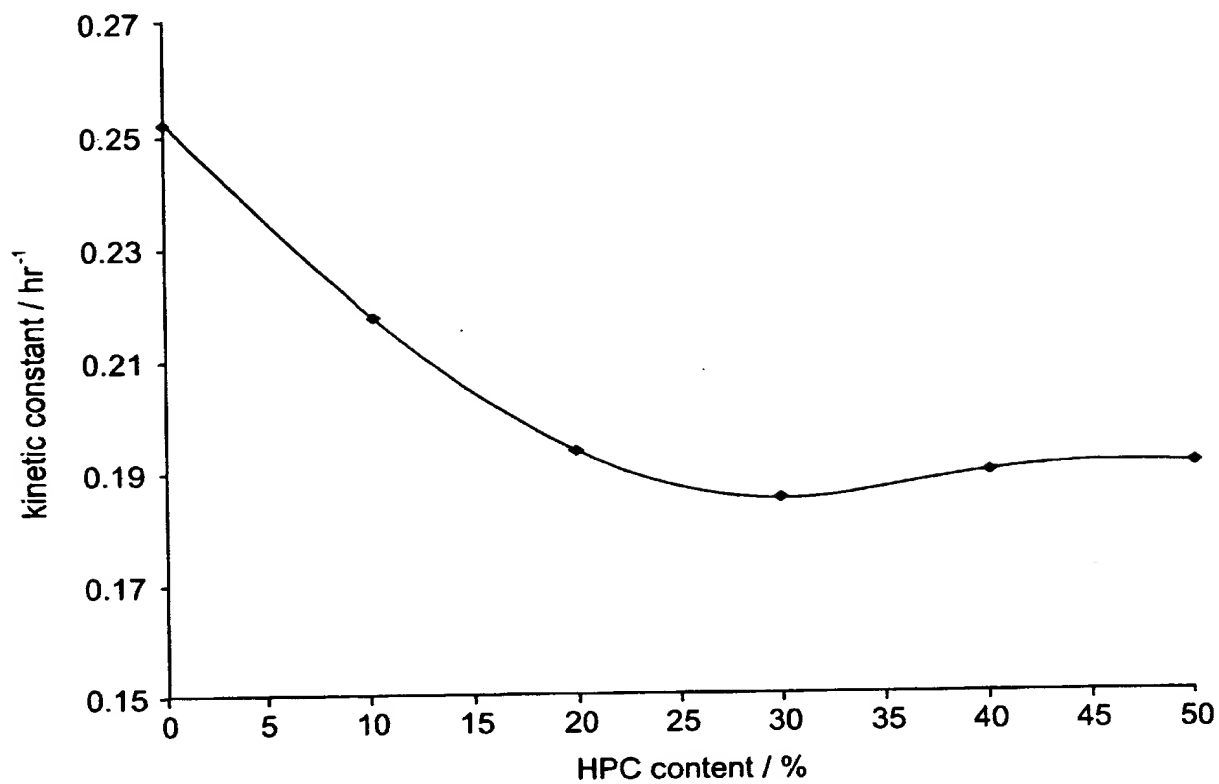
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*Fig. 7*

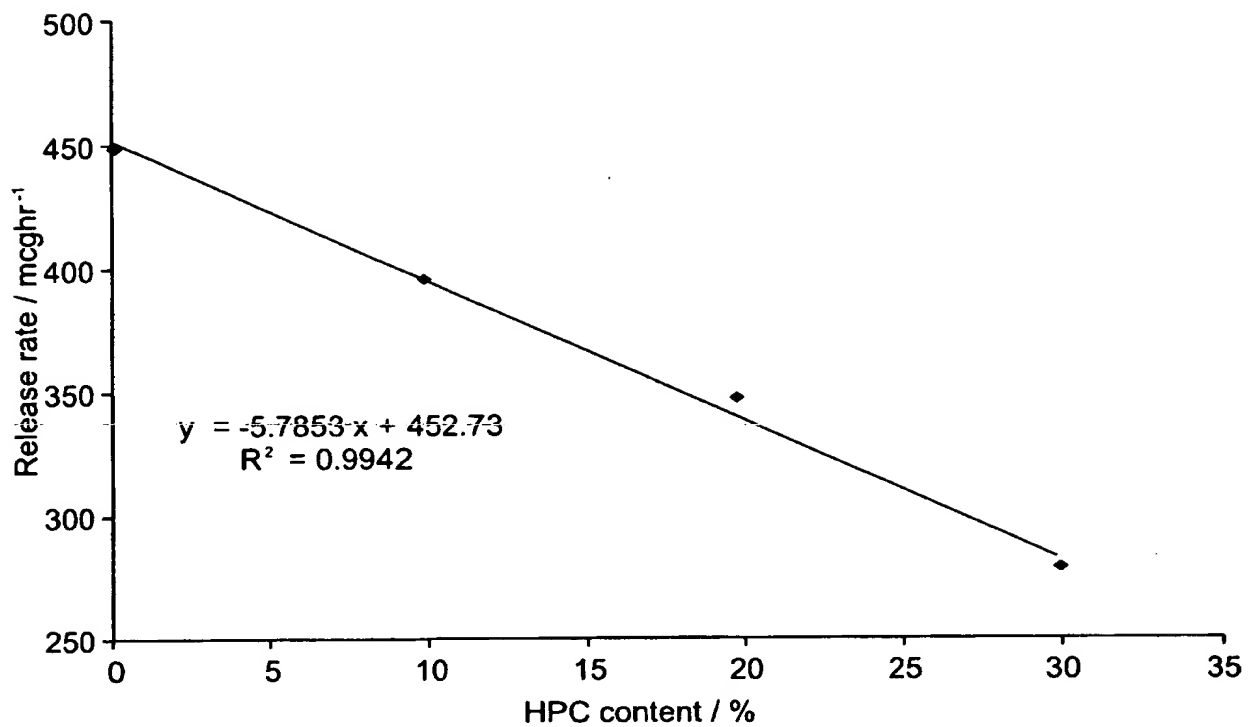
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*Fig. 8*

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*Fig. 9*

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*Fig. 10*

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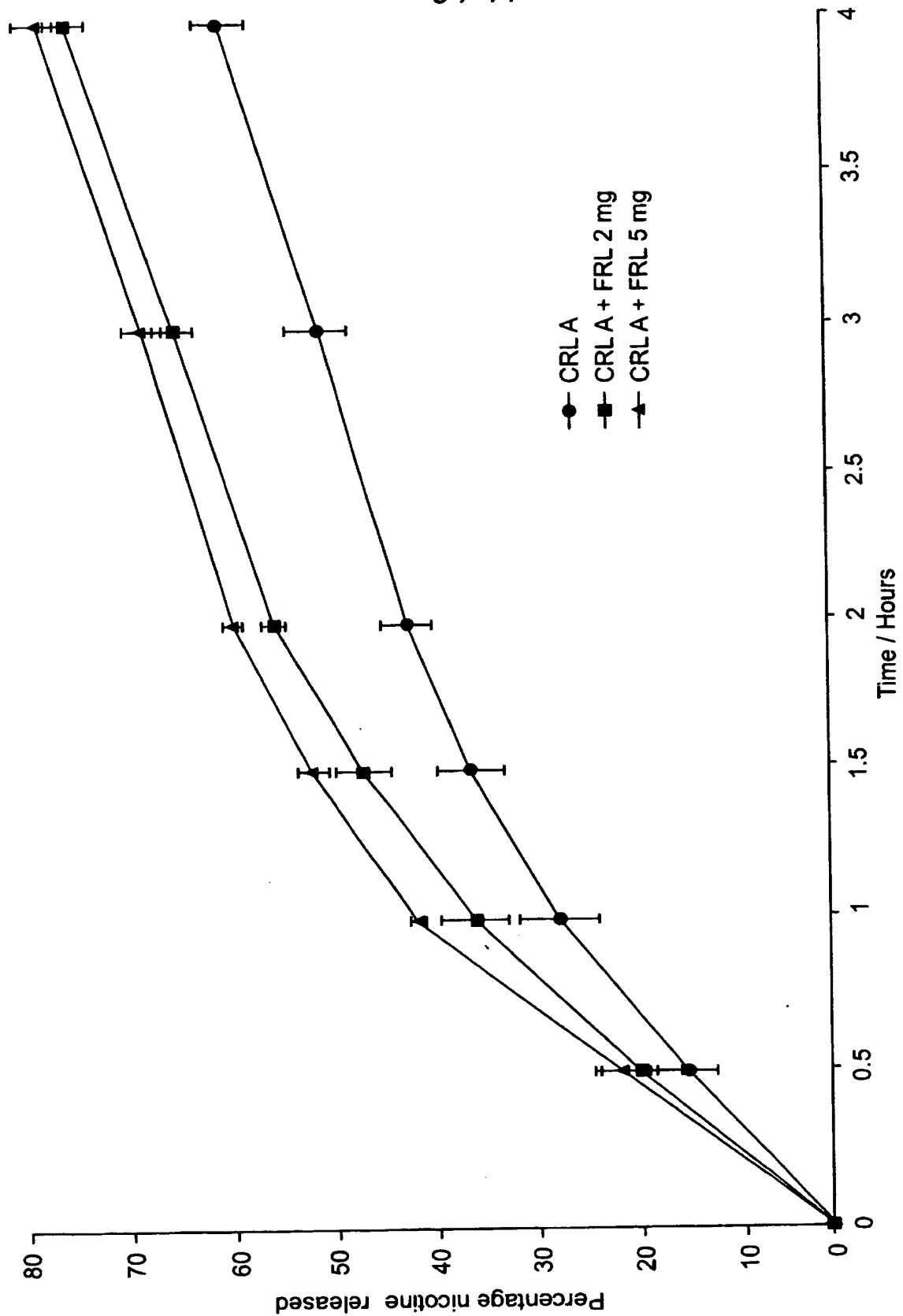
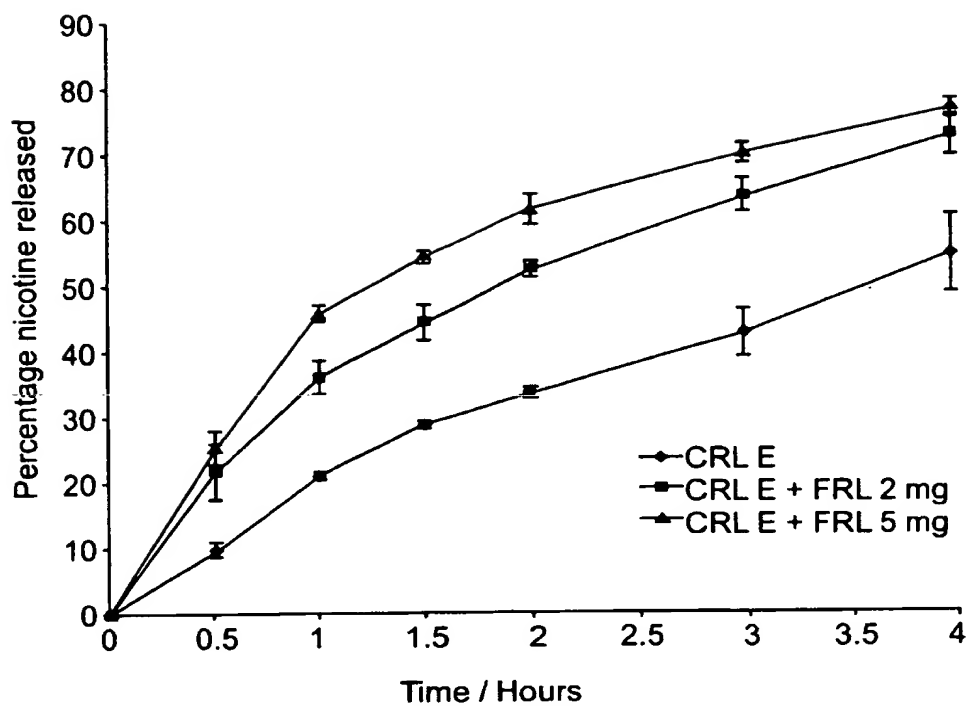


Fig. 11

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*Fig. 12*

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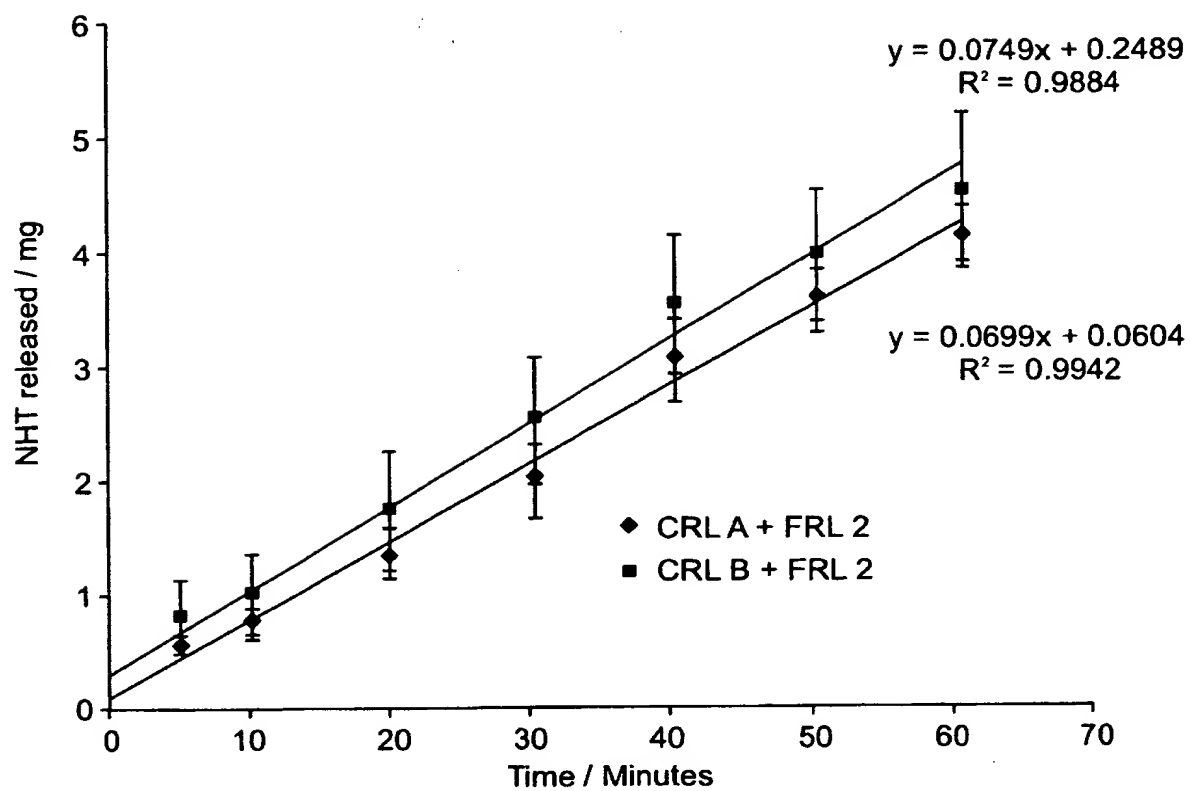


Fig. 13

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04428

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/24 A61K31/465

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BIOSIS, CHEM ABS Data, EMBASE, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>US 5 879 710 A (BROMET NORBERT E) 9 March 1999 (1999-03-09)</p> <p>column 1, line 12 - line 21 column 3, line 58 -column 4, line 2 column 4, line 33 - line 37 column 4, line 50 -column 5, line 5; claims 1,2,6; example 1; tables 1,2 --- -/--</p>	<p>1-8, 12-14, 16-23, 25, 27-33,36</p>

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

27 February 2001

Date of mailing of the international search report

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INTERNATIONAL SEARCH REPORT

National Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LEE Y ET AL: "Oral mucosa controlled delivery of LHRH by bilayer mucoadhesive polymer systems" JOURNAL OF CONTROLLED RELEASE, NL, ELSEVIER SCIENCE PUBLISHERS B.V. AMSTERDAM, vol. 37, no. 3, 1 December 1995 (1995-12-01), pages 251-261, XP004037428 ISSN: 0168-3659 page 252, left-hand column, line 4 - line 31 page 252, right-hand column, last paragraph; table 1 page 253, right-hand column, last paragraph -page 254, left-hand column, paragraph 1 page 254, left-hand column, last paragraph -page 255, right-hand column, paragraph 1; figure 2 page 260, line R, paragraph 2</p>	<p>1-7, 10, 12-14, 16-23, 25, 27-32, 35, 36</p>
X	<p>US 5 236 713 A (WATO TAKAHIKO ET AL) 17 August 1993 (1993-08-17)</p> <p>column 2, line 18 - line 24 column 2, line 34 - line 48 column 3, line 13 - line 41 column 3, line 54 - line 59 column 3, line 37 -column 4, line 25; claims; examples</p>	<p>1-8, 12-14, 16-23, 25, 27-33, 36</p>
X	<p>WO 98 46235 A (FIERUS MONIKA ;NEUSER DIETER (DE); BAYER AG (DE); WIEHL WOLFGANG () 22 October 1998 (1998-10-22)</p> <p>page 1, paragraph 1 page 1, paragraph 3 - paragraph 4 page 3, last paragraph -page 4, paragraph 1; claims; examples</p>	<p>1-3, 10-13, 15, 17-19, 21, 24-26, 35, 36</p>
A	<p>WO 92 01445 A (ALZA CORP) 6 February 1992 (1992-02-06) page 5, paragraph 1 - paragraph 4 page 5, last paragraph -page 6, paragraph 2 page 6, last paragraph -page 7, line 1; claims 1,2,9,12,13,18-20; figures 1,5; examples</p>	<p>1-36</p>

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 00/04428

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	<p>WO 00 13662 A (HENNINGFIELD JACK E ;CONE EDWARD J (US); JSR LLC (US); PINNEY JOHN) 16 March 2000 (2000-03-16) page 6, last paragraph -page 7, line 1 page 71, line 21 -page 8, line 14 page 9, line 20 - line 26 page 9, line 29 -page 10, line 25; figures page 16, line 8 - line 29 page 24, line 12 -page 25, line 29; claims; examples</p> <p style="text-align: center;">---</p>	<p>1-3,7,9, 10,17, 18,34</p>
T	<p>PARK C R ET AL: "Formulation of a bilayer buccal adhesive tablet for nicotine replacement therapy." JOURNAL OF PHARMACY AND PHARMACOLOGY, vol. 52, no. Supplement, September 2000 (2000-09), page 303 XP000982579 137th British Pharmaceutical Conference;Birmingham, England, UK; September 10-13, 2000 ISSN: 0022-3573 the whole document</p> <p style="text-align: center;">-----</p>	<p>1-36</p>

INTERNATIONAL SEARCH REPORT

Information on patent family members

National Application No

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